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CONTENTS

BEDREST STUDIES - METHODS AND INSTRUMENTATION

By Fred B. Vogt, M.D.
Texas Institute for Rehabilitation and Research

INTRODUCTION

The observations of signs and symptoms of orthostatic cardiovascular instability in astronauts Schirra and Cooper, as well as the changes observed in Russian cosmonauts after orbital spaceflights, have increased the concern as to man's ability to withstand prolonged exposure to zero gravity conditions. Some of the changes observed had been predicted on the basis of bedrest and water immersion studies. But, there are many conditions that occur in association with a spaceflight such as weightlessness, physical inactivity, stress, and dehydration which could have accounted for the observed cardiovascular instability. The difficulty of interpreting data acquired in association with spaceflights stems from at least four basic limitations: (a) the small number of physiological measurements that can be made, (b) the small number of subjects per flight, where there is available only an $\underline{n}$ of one or an $\underline{n}$ of two, (c) the inability to maintain a controlled experimental situation, and (d) the inability to perform on-the-ground studies to simulate all aspects of space flight.

At the present time it is impossible to extrapolate from the experimental laboratory to the situation of space flight to interpret properly the flight observations which have been made. In fact, it is impossible to extrapolate the findings from one bedrest study to another, or from one experimental circumstance, such as bedrest and water immersion, to another. Our lack of knowledge and inability to do this stems from several factors: (a) a lack of understanding of the day-to-day variations in measurements and responses of a normal individual, (b) the difficulty of performing adequately controlled experiments on human subjects, (c) the small number of bedrest and water immersion studies which have been performed to date, (d) the possibility of different physiological mechanisms of deconditioning producing the same outward signs and symptoms, and (e) the difference in methodology and instrumentation used in various experiments. Our goal at Texas Institute for Rehabilitation and Research has been to overcome as many of these problems as possible. By performing additional studies in which meaningful measurements were made frequently enough and in a standardized manner, we hope eventually to arrive at the

mechanism of the deconditioning which occurs. Only the initial steps have been made and it may take several years to achieve the final goal.

Bedrest studies were begun at the Texas Institute for Rehabilitation and Research in March 1963, on six subjects to investigate the potential effect of periodic Flack maneuvers in preventing or lessening the cardiovascular deconditioning found after 3 days of bedrest. In the summer of 1963, two 3-day and two 14-day bedrest studies were conducted on groups of six subjects to evaluate the effect of isometic exercise. In the summer of 1964, three 10-day bedrest studies were conducted on 10 subjects to evaluate the effect of periodic inflation of leg cuffs on the lower extremities, or the effect of a moderate amount of "isotonic" exercise in preventing cardiovascular deconditioning of bedrest. In addition, two water-immersion experiments were performed on a group of four subjects and are reported elsewhere in these conference proceedings. The data from the last bedrest studies are too voluminous to have reduced and analyzed at present. It is the purpose of this presentation to describe the methodology and experimental design of the bedrest studies conducted at the Texas Institute for Rehabilitation and Research in the summer of 1964.

METHODS

Calendar of Experimentation

The calendar of experimentation for the studies conducted in the summer of 1964 is shown in figure 1. Three 10-day bedrest periods are indicated. During recumbency period number 1, half of the subjects had cuffs applied to their lower extremities to serve as a potential preventive measure, and the other half of the subjects performed a routine of periodic "isotonic" exercises. During recumbency period number 2, the subjects who previously had cuffs performed exercises, and the group who had performed exercises had cuffs applied to their extremities. During recumbency period number 3, all of the 10 subjects were exposed only to the 10-day period of bedrest. The cuffs were applied to the proximal part of both lower extremities and were inflated to a pressure of 77 mm Hg with a cycle of 5 minutes on, 10 minutes off, for the entire duration of the 10-day bedrest period. Control data was collected on the subjects during the 10-day period preceding the first period of recumbency. A 3-week interval was allowed between bedrest periods to assure that the subjects had recovered from the deconditioning that occurred with each period of recumbency. The subjects were submitted to bedrest in two groups separated by one day to allow for performance of a complete tilt-table test on the day immediately preceding bedrest as well as on the final day of bedrest. Numerous other testing procedures were carried out on the subjects periodically and are indicated on the following pages.

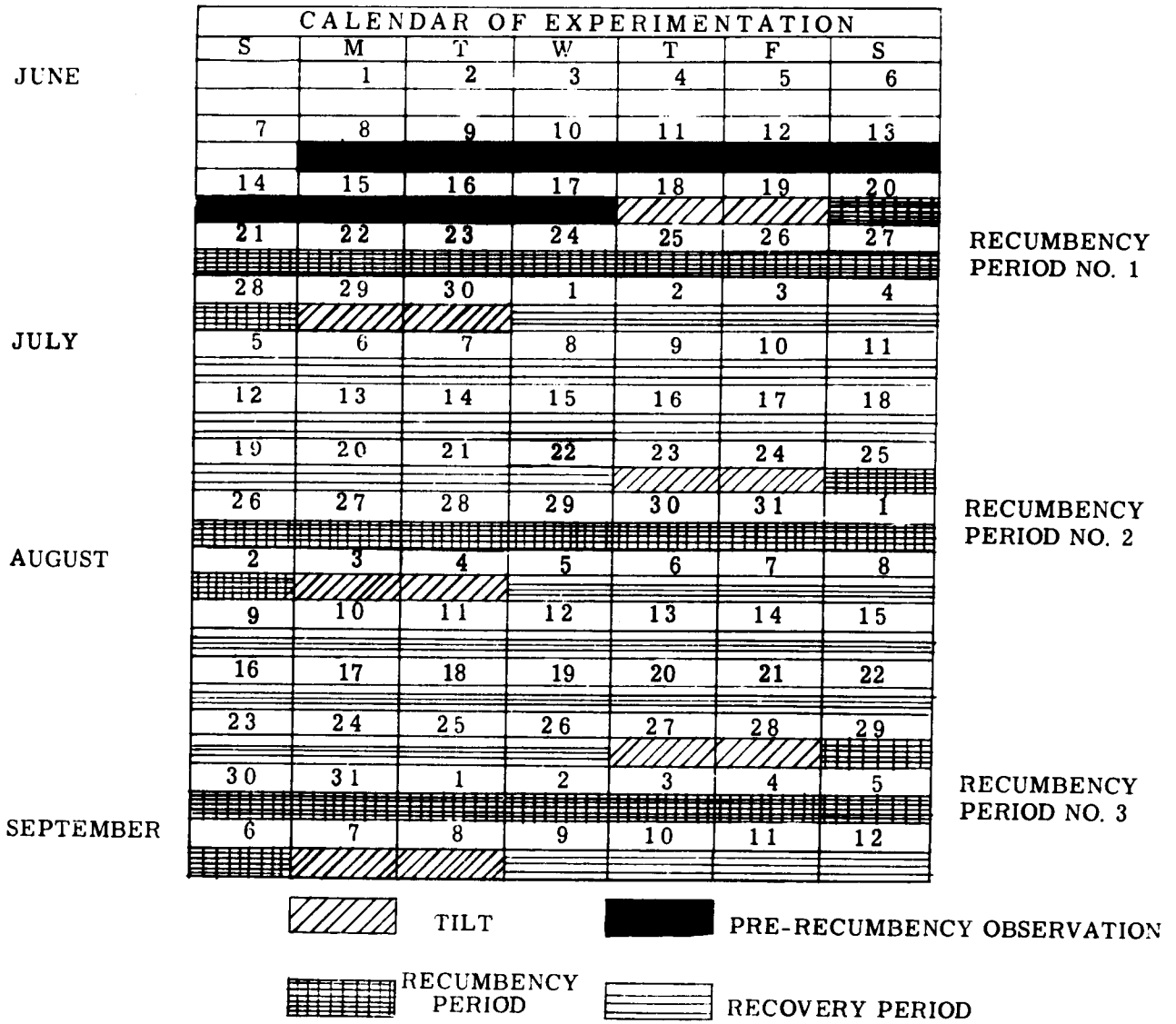

Figure 1.- Calendar of experimentation.

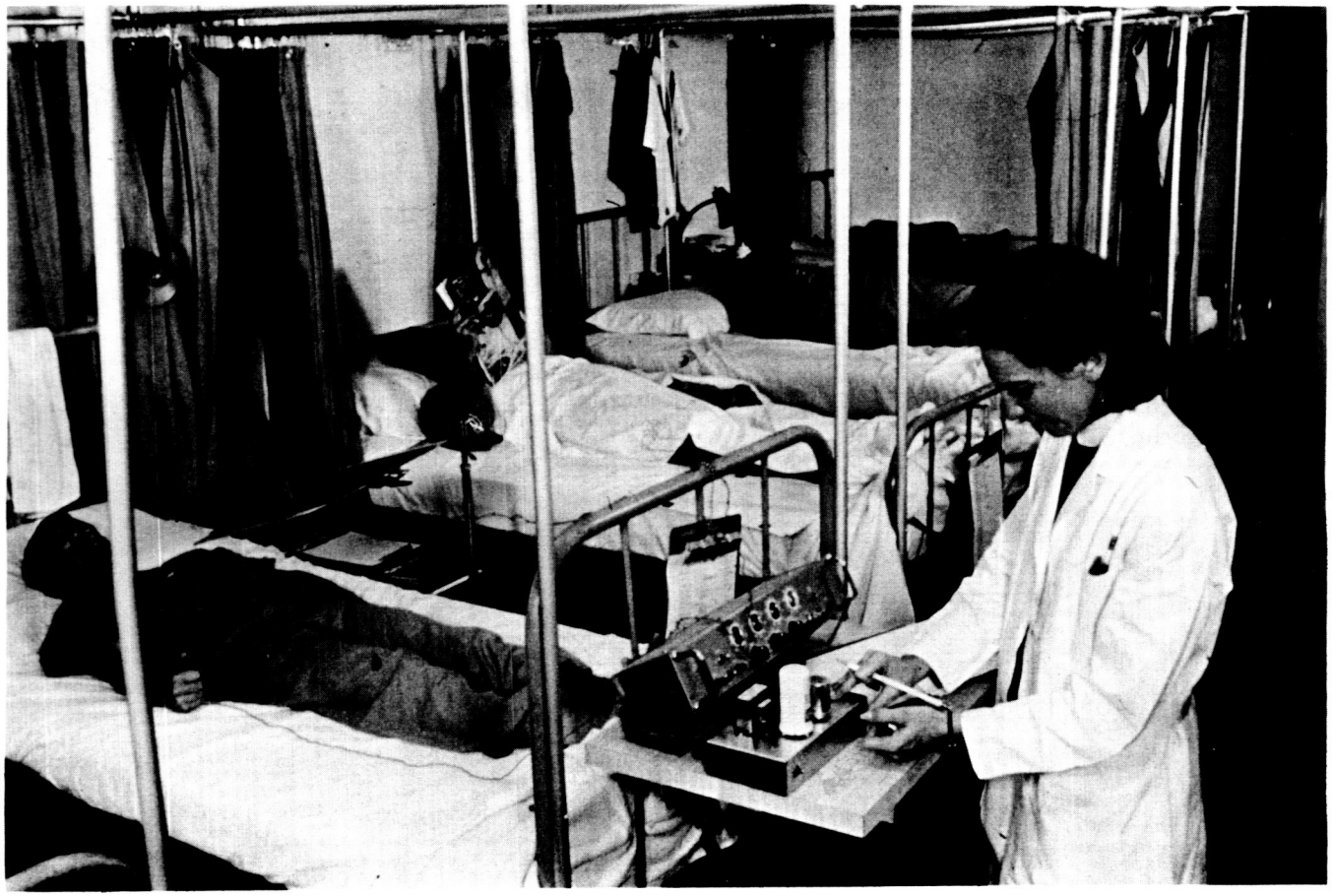

Figure 2.- View of experimental ward.

Subjects

Eleven healthy adult males were utilized as experimental subjects. Nine of the subjects participated in all three periods of recumbency; one subject participated in only the first period of recumbency and was replaced by another who participated in the last two periods. The subjects were selected from the local college population and their ages ranged from 21 to 25 years. Each potential subject was given a complete medical history and physical examination and a simple tilt-table test before selection as a subject. Fainting on a preliminary tilt-table test (20 minutes duration) ruled out the selection of a prospective subject. Fees of 10 dollars per day during routine testing and recovery periods, and 30 dollars per day during the bedrest period were paid to the subjects. The subjects were admitted to the Texas Institute for Rehabilitation and Research as hospital patients for experimental studies. The details of the experiment and the risk involved were explained to them in detail prior to the start of the study.

Experimental Conditions

1. Ward Area.- The subjects were housed in an experimental ward for the entire duration of the experimental study. Figure 2 shows a view taken from one end of the ward. Privacy for individual beds was provided by means of a curtain which circled each bed. Environmental conditions were controlled by the usual hospital environmental control mechanisms. Temperature, humidity, barometric pressure, and a lighting schedule were controlled and recorded.

2. Activities.- During the pre-bedrest and recovery periods, the subjects were encouraged to follow a routine approximating that prior to becoming a subject. The subjects spent every night in the ward, including the nights of the recovery periods. Athletes were allowed to participate in an active training schedule if they had followed one previously. Except for the times of testing, eating, and urine collection periods, the subjects were free to come and go from the hospital. The record of activities performed was kept on an hourly basis according to a daily activity sheet.

The subjects were required to remain in bed during the bedrest periods. They were given one pillow for use under their heads, were allowed to turn in bed and roll from side to side, and were allowed to feed themselves by turning on their sides in bed. They were not allowed to sit in bed or to get up for bathroom privileges. Subjects were supervised by a physician during the bedrest periods, and a physician was on call during all other times of the study. Two orderlies assisted in subject care during the day, and one assisted at night.

3. Meals.- The subjects were given a standard hospital kitchen diet and were required to eat all food that was served to them. The food trays were prepared and weighed to provide each subject with an identical diet. The dietary content of sodium chloride approximated 10 grams daily. An additional food tray was prepared and sent to the laboratory for analysis for sodium and potassium content. No food or beverages were allowed during the times the subjects were away from the hospital. The subjects were allowed to drink distilled water ad libitim, but a strict record of intake was maintained.

4. Laboratory.-

a. Upon admission to the hospital, each subject had a routine chest X-ray, serology, CBC, urinalysis, and electrocardiogram.

b. Periodic serum sodium and potassium determinations were made.

c. Urine was collected in 6-hour collection periods which began at 1 a.m. over the entire duration of the study. Sodium, potassium, and osmolality determinations were made on each 6-hour sample for each subject. A total 24-hour aliquot was also obtained and analyzed for sodium and potassium. Urine was collected and preserved for the determination of 17-hydroxycorticoids and catecholamines on the same 6-hour samples.

d. Food was pooled for a 24-hour period and analyzed for sodium and potassium content.

e. Feces were pooled for a 4 to 5 day collection period and analyzed for sodium and potassium content.

f. Radioisotope studies to determine plasma volume, extracellular fluid space, total body water, and red cell mass were made on days 1, 4, and 10 of each bedrest period.

5. Leg Circumference.- Measurements of leg circumference at three sites on each leg were made twice daily, in the morning and the afternoon. These measurements were performed using a flexible measuring tape which was wrapped around previously determined marks on the legs to assure that the same sites were measured at all times.

6. Body Weight.- Each subject was weighed daily in the early morning after emptying his bladder. During the periods of bedrest, weights were obtained by means of a platform scale rolled to each bedside so that the subjects could maintain a horizontal position.

7. Phychological Testing.- Personality assessment prior to the experimental program included Cattell's 16 PF, Guilford's Activity Dimension, and the Thematic Apperception Test. A test battery consisting of:

(1) simple reaction time, (b) aiming, (c) visualization, (d) number facility, and (e) speed of closure were administered immediately preceding and following each passive tilt procedure and on the fourth day of bedrest. The Holtzman Inkblot Test and an alternating perspective measure were administered on days 2, 6, and 10 of bedrest. Tests of time perception, word fluency, and responses to the Clyde Mood Scale were obtained twice daily. At the conclusion of each period, responses to an immobilization questionnaire were obtained from the subjects. In addition, ranking of the subjects was obtained from independent observers along four dimensions: (a) sociability, (b) arousal, (c) attitude toward the experiment, and (d) affective expression.

8. Testing and Data Analysis.- Three basic provocative tests were used to evaluate the responsiveness of the cardiovascular system to changes in the subject condition, level of work performance, and ability to adjust to the upright postural orientation. These tests included the bicycle ergometry, Erkin exercises, and passive tilt procedures, as well as the measurements which were described above. Measurements were made and recorded using an instrumentation system provided and constructed by the Space Medicine Branch - Bioinstrumentation Section of the National Aeronautics and Space Administration. Data reduction and analysis are presently being performed in cooperation with the Biomathematics and Computer Facility of Baylor University College of Medicine, the personnel of the Texas Institute for Rehabilitation and Research, the Texas A & M Computer and Statistics Laboratory, and the personnel and equipment of the Data Systems Branch at the National Aeronautics and Space Administration. A detailed description of the above subject matter follows in the form of topic descriptions.

BIOINSTRUMENTATION

A bioinstrumentation system was designed to collect multiple channels of physiological data that might describe the cardiovascular deconditioning of bedrest as measured during tilt-table procedures, bicycle ergometry, or during Erkin exercise procedures. It was required that there be processing units for a multitude of sensor inputs, and that measurements could be made from any of several central experimental areas, or from the bedside of an individual subject during the period of recumbency. A moveable signal conditioner unit which could be rolled to the test area was connected by wire to a central monitoring console at which monitoring and recording equipment were located. Figure 3 shows a block diagram of the instrumentation system. Figure 4 shows a picture of the actual instrumentation system with the portable rack of signal conditioners located at the left.

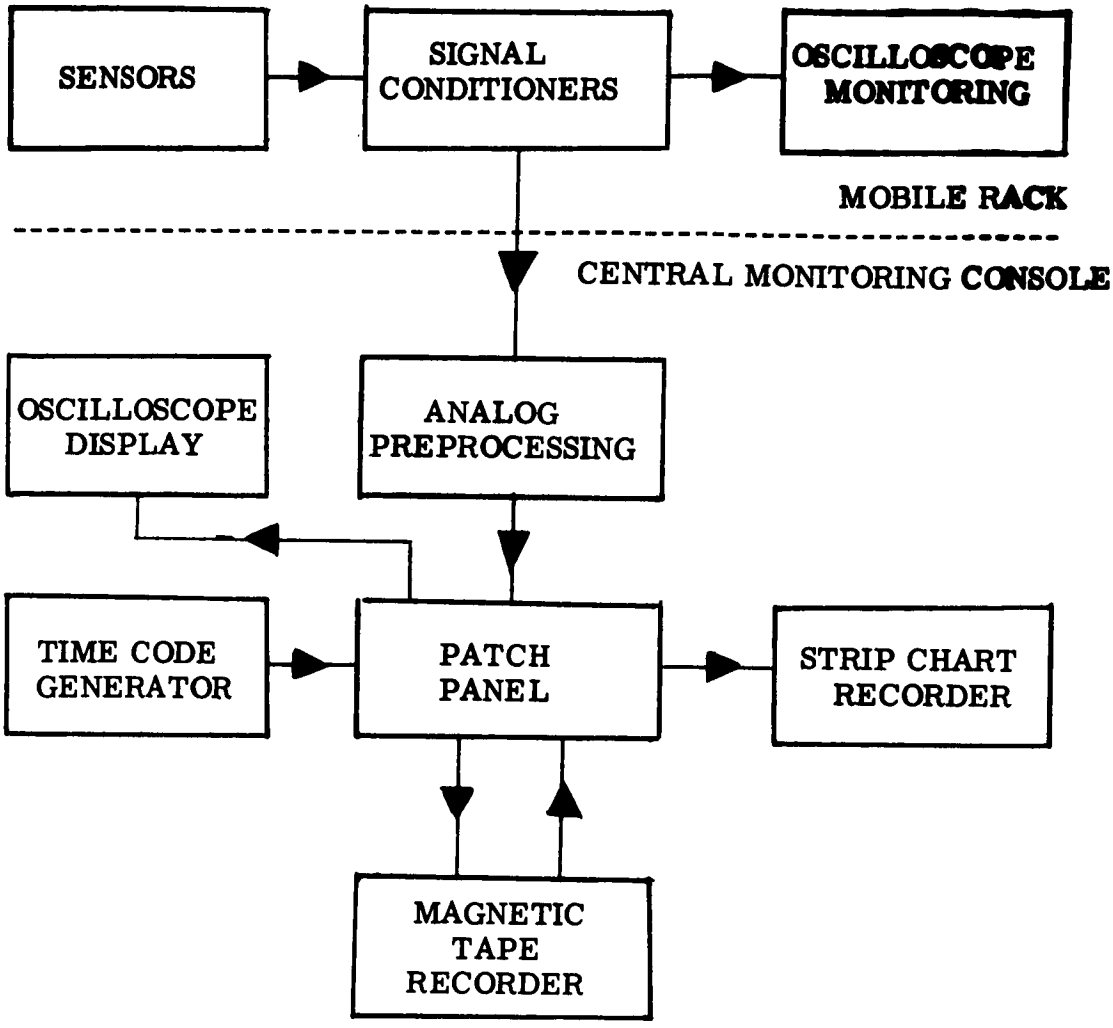

Figure 3.- Block diagram of bioinstrumentation system.

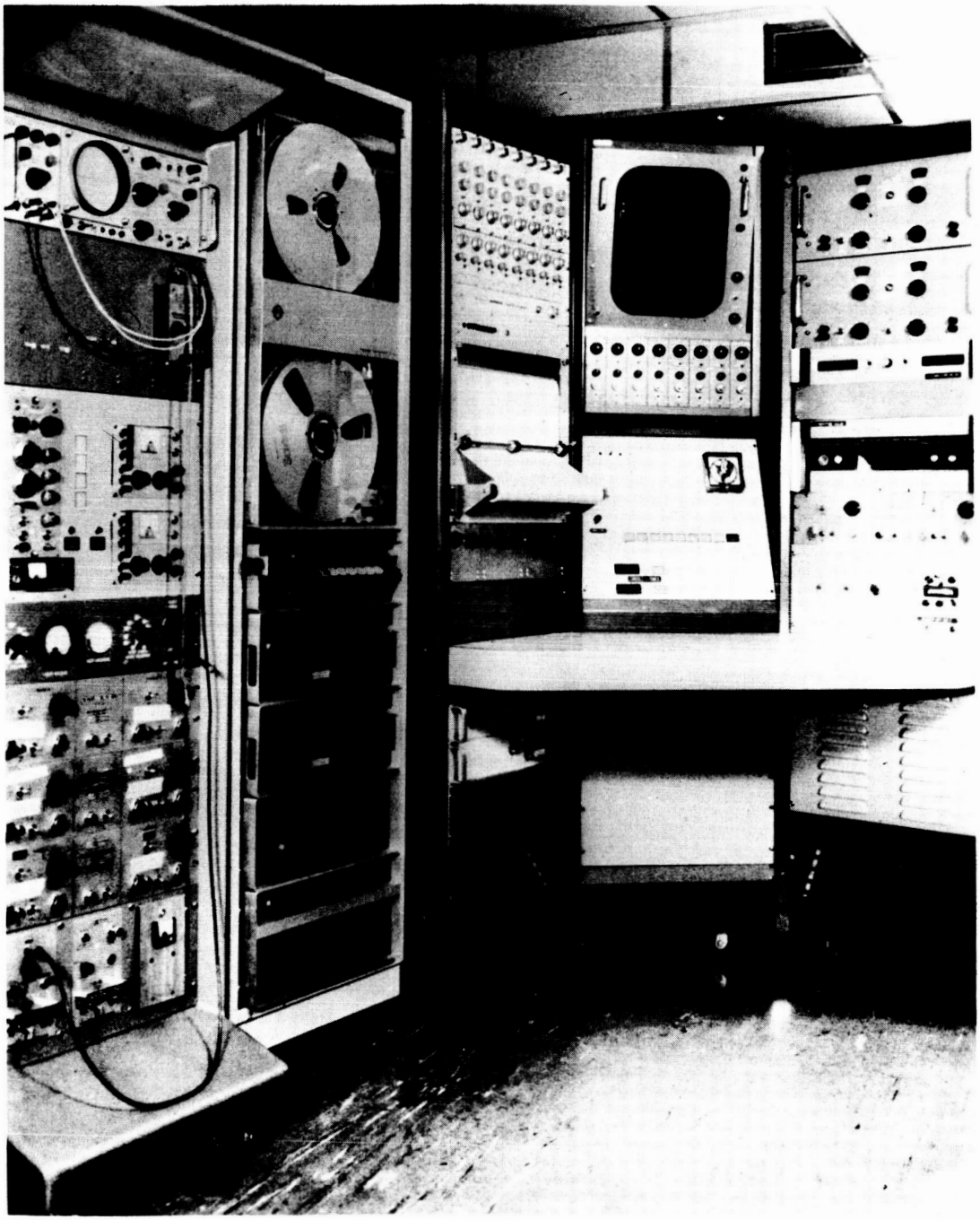

Figure 4.- Bioinstrumentation system.

The sensor inputs available allowed for a variety of measurements. Intra-arterial blood pressure was obtained using a Statham pressure transducer connected to the central unit through a Sanborn Carrier pre-amplifier. Indirect arterial blood pressure was obtained by a cuff-microphone technique which employs an E & M Company cuff-inflator system to provide automatic cycling of the cuff inflation and deflation every 30 seconds. Leg circumference measurements were made using a Whitney mercury-in-rubber strain gauge connected to a Parks Electronic amplifier unit. Respiration was measured by means of an impedance pneumograph. Precordial vibrations were measured by means of a capacitance type of microphone operated into a Ling-Temco-Vought amplifier. The electrocardiogram and impedance pneumogram were detected by means of NASA skin electrodes attached to the skin with an Eastman 9-10 glue or double-back colostomy tape. Electrocardiogram and electromyogram signals were amplified by means of conventional difference type of amplifiers. A Frank Lead system was used to provide the orthogonal vector components to represent the cardiac electrical activity. Each input signal to the portable unit could be observed on a rack-mounted monitor oscilloscope located on the unit. The remote central monitoring console, with the recording apparatus, could be controlled from this portable unit.

To the right of figure 4 is shown the central monitoring unit to which signals were routed by means of wire from the portable monitoring unit. A patch panel matrix located in the central monitoring console was used for routing signal flow and for programing all control logic and signal processing to and from the tape recorder. The patch panel was used also to route signals to the oscilloscope, to the strip-chart recorder, and to and from special processing units such as band-pass filters or cardiotachometer units.

An 8-channel Sanborn oscilloscope was used for simultaneous display of multiple signals, and could be connected to either the input or the output of the tape recorder. The oscilloscope provided a convenient means of monitoring signals while sensors were placed. During the course of the experiment, it helped assure good quality of the recordings without having to make a direct strip-chart recording. However, a strip-chart recorder was available for use during the experiment, or for playback of data from selected portions of the magnetic tape at a later time. The strip-chart system used was an Offner Dynograph 8-channel pressurized ink-writing system which is mounted in the central monitoring console as shown in figure 4. Also included in the central unit, at the extreme right, are 2 Krohn-Hite band-pass filters and a coder-searching apparatus. The coder-searcher unit is an EECO unit which provides IRIG type B format which is recorded on a direct electronics channel of the magnetic tape system. In addition, the unit provides a low frequency BCD type of output which can be recorded on magnetic tape or read out directly on a strip-chart recorder to identify with 1-second times corresponding to the IRIG type B format. The coder-searcher capability enables rapid and automatic

location of data from a given tape by reference to log sheets and code sheets made at the time of recording. The magnetic tape recorder provided 13 channels of FM record capability, 1 channel of direct record, and 2 side track channels for voice recordings. For most of the recording done in the study, a speed of $1\frac{7}{8}$ inches per second, using double band width electronics, allowed for an upper frequency response of 625 cps.

BICYCLE ERGOMETRY

Described elsewhere by Dr. David Cardus.

ERKIN EXERCISES

Described elsewhere by Dr. Willie C. Beasley.

PASSIVE TILT PROCEDURES

Comprehensive head-up passive tilt procedures were conducted on the subjects immediately before and after the 3 periods of recumbency. In addition, simple tilt procedures were determined weekly during the pre-bedrest period and during the recovery periods to determine the individual's day-to-day pattern of response to the tilt-table test.

The simple tilt differed from the comprehensive tilt study in that only one lead of ECG was obtained and blood pressure was obtained by a cuff-microphone technique rather than by direct arterial puncture. The procedure used in performance of comprehensive held-up tilts was as follows:

1. The subjects were kept n.p.o. for several hours prior to the tilt-table test to protect against regurgitation and aspiration of foods should fainting and an associated vagal response occur. It was found desirable to allow the subjects to drink a glass of milk several hours before the tilt procedure so that they would not be hungry at the time the tilt-table test was performed.

2. The subject was fitted with appropriate sensors prior to being placed on the tilt table.

3. Measurements during the tilt-table test included the following:

(a) Frank Lead System Vectorcardiogram

(b) Impedance pneumogram

(c) Intra-arterial blood pressure from the right brachial artery

(d) Right and left leg calf circumference by a Whitney mercury-in-rubber strain gauge

(e) Precordial vibrations by means of Ling-Temco-Vought capacitance type of microphone

(f) Venous pressure from the left forearm by means of a venous intra-catheter connected to a Statham pressure transducer

(g) Forearm circumference changes by means of a Whitney mercury-in-rubber strain gauge connected to a Sanborn amplifier

4. An emergency cardiac drug tray, defibrillators, cardiac pacemaker, artificial respiration equipment, and atropine drawn into a syringe was kept available for any cardiac emergency.

5. A motorized tilt table with an English saddle type of support was used to tilt the subjects from 0 to 70° in 30 seconds. Provision was made to release the gear mechanism for instantaneous tilt-down with the occurrence of syncopal or vagal type of reactions.

6. Arterial blood samples were obtained during a 2-minute period from each subject prior to tilting while expiratory gases were collected in a Douglas bag.

7. An I^{131} plasma volume was determined prior to tilting and hematocrit and hemoglobin determinations were made before and after the tilt procedure.

8. A Flack procedure was performed 5 minutes prior to and 5 minutes after tilting the subject to the 70° upright position. Figure 5 shows the basic tilt procedure used. The subjects were instrumented completely for the tilt procedure, after which 5 minutes of control data were acquired prior to performing the first Flack test. The Flack maneuver consisted of blowing to a pressure of 40 mm Hg into a Flack device for exactly 15 seconds. Five minutes of data then were collected before the subject was tilted to the 70° head-up position. The subject was kept in the 70° position for 20 minutes unless syncope or impending syncope occurred; in which case, he was tilted down immediately. After tilt-down to the horizontal position, 5 minutes of data were obtained prior to performance of a second Flack maneuver. A final 5 minutes of data

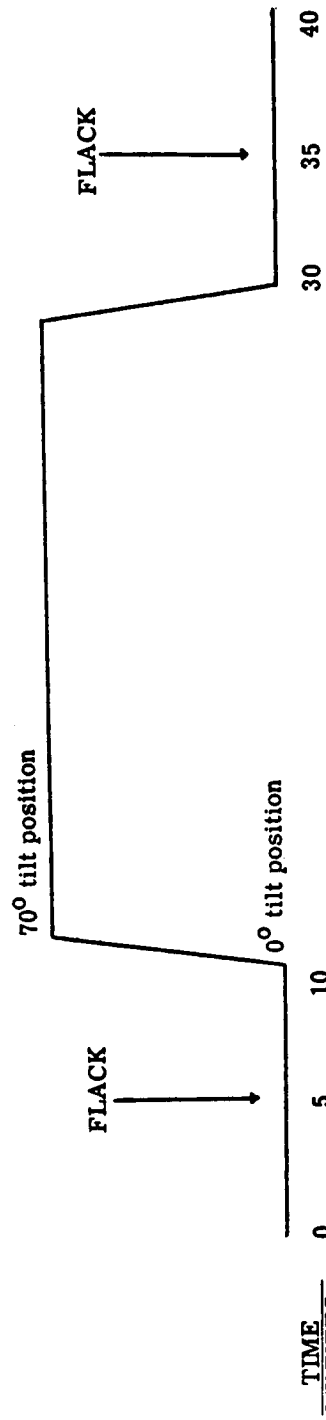

Figure 5. Basic Tilt Procedure Showing Time of Flack Maneuvers, Tilt Up and Tilt Down

were obtained after the Flack test. If the subject had syncope or impending syncope, and was tilted down, a 10 to 20 minute recovery period was allowed before tilting him a second time. This second tilt was done to provide information on the reproducibility of a tilt procedure on a given day.

Figure 6 shows a picture of a subject on the tilt table prior to being tilted to the upright position. Figure 7 shows the technique of support of the subject while he is tilted to the 70° position. Figure 8 shows a code sheet used for tilt-table studies to record observations made during the study, and to document the time of occurrence of the various tests performed. Each sheet allows for identification of the magnetic tape, test date, subject number, time of day, experimental circumstance, and the EECO code corresponding to the time of the magnetic tape.

9. Measurements of forearm blood flow, venomotor tone, and peripheral vascular resistance were determined as follows. The forearm circumference change to venous occlusion was determined by the method of Whitney which used a mercury-in-rubber strain gauge. Venous pressure was measured through a polyethylene catheter passed into the large forearm vein such that the tip of the catheter was located approximately 1 centimeter distal to the mercury-in-rubber strain gauge. Figure 9 shows the placement of the apparatus for making these measurements. On the proximal portion of the arm is located the venous occlusion cuff, and at the wrist on the distal portion of the arm is located the arterial occlusion cuff. Mean arterial blood pressure was obtained continuously from a needle in the brachial artery of the opposite arm as shown in figure 10. From the simultaneous measurement of the forearm plethysmograph, mean arterial blood pressure and venous pressure and response to venous occlusion, calculation of forearm blood flow, forearm vascular resistance, and a type of venomotor tone were made.*

Two complete determinations were made at least 5 minutes apart prior to the tilt. Measurements for forearm blood flow were made at 1 minute, 2 minutes, 4 minutes, 6 minutes, 8 minutes, 10 minutes, 14 minutes, and 18 minutes of the 70° head-up tilt procedure. Since the position of the arm was not changed during the tilt procedure, venomotor tone measurements were not thought to be valid during the tilt because of the effect of venous stasis on pressure volume relationships. Determinations of venomotor tone were made immediately after tilting down and at 2 minutes, 4 minutes, and 8 minutes after the tilt-down procedure.

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*J. Clin. Investigation. 43:532, 1964

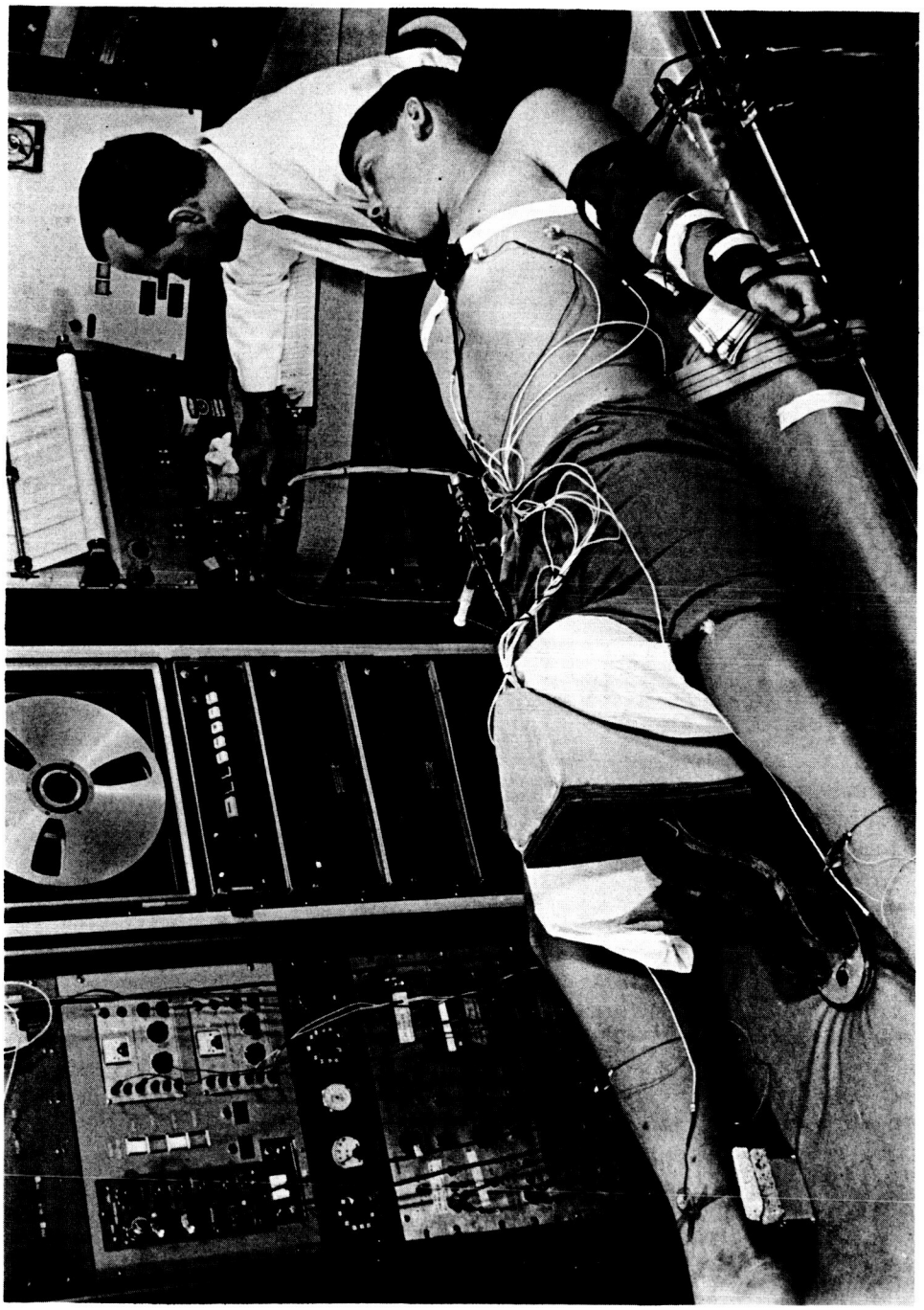

Figure 6.- Subject on tilt-table prior to tilting.

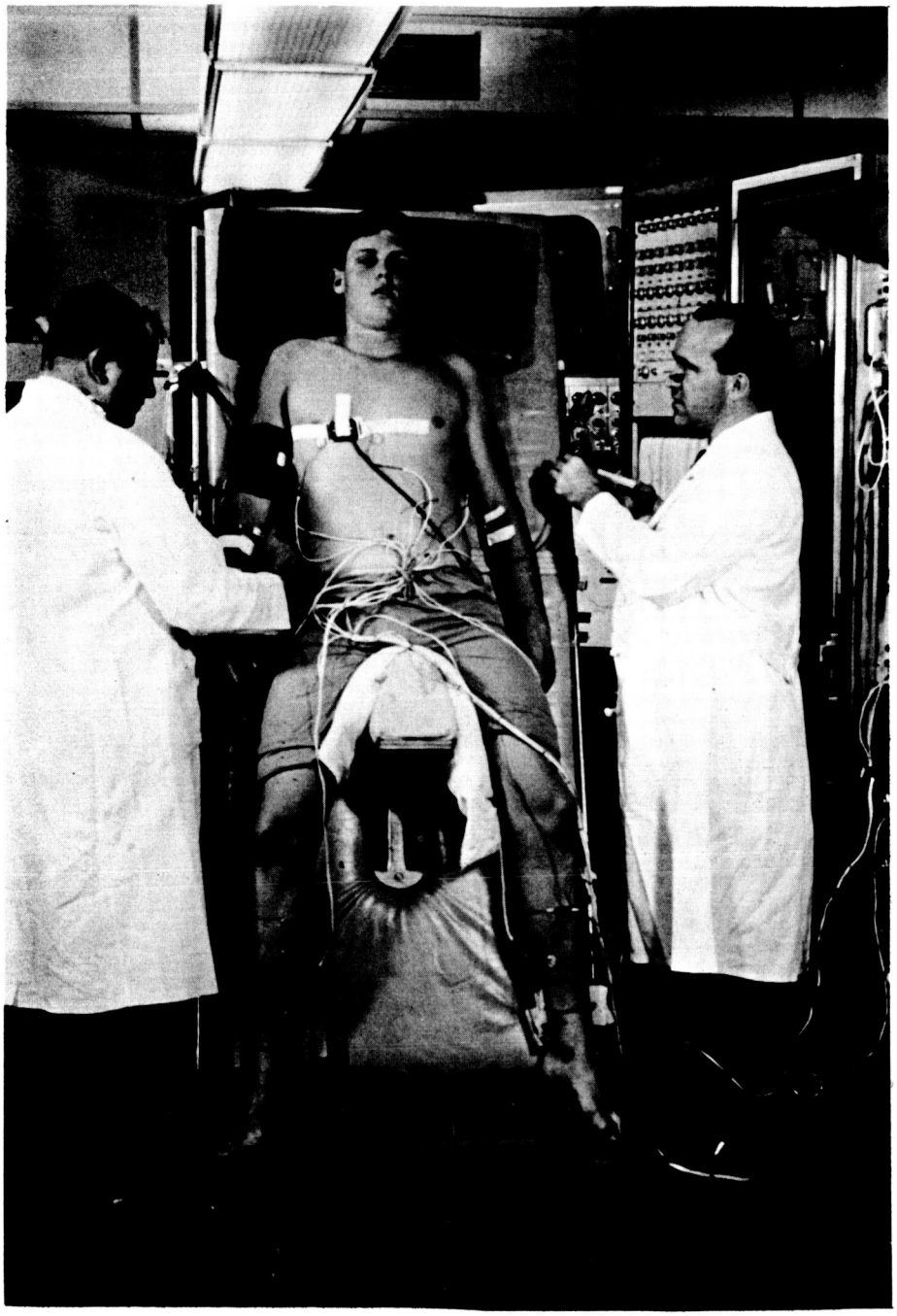

Figure 7.- Subject in 70° passive tilt showing English saddle support.

Page _____

CODE SHEET

TILT TABLE STUDIES

DATE _____ MAGNETIC TAPE NO. _____

SUBJECT	TIME OF DAY	EECO CODE			EXPERIMENTAL CIRCUMSTANCE
		Hr	Min	Sec	

OBSERVER _____

STRIP CHART (OFFNER ETC.) RECORD MADE SIMULTANEOUSLY? YES___ NO___

Figure 8.- Code sheet for use with tilt-table studies.

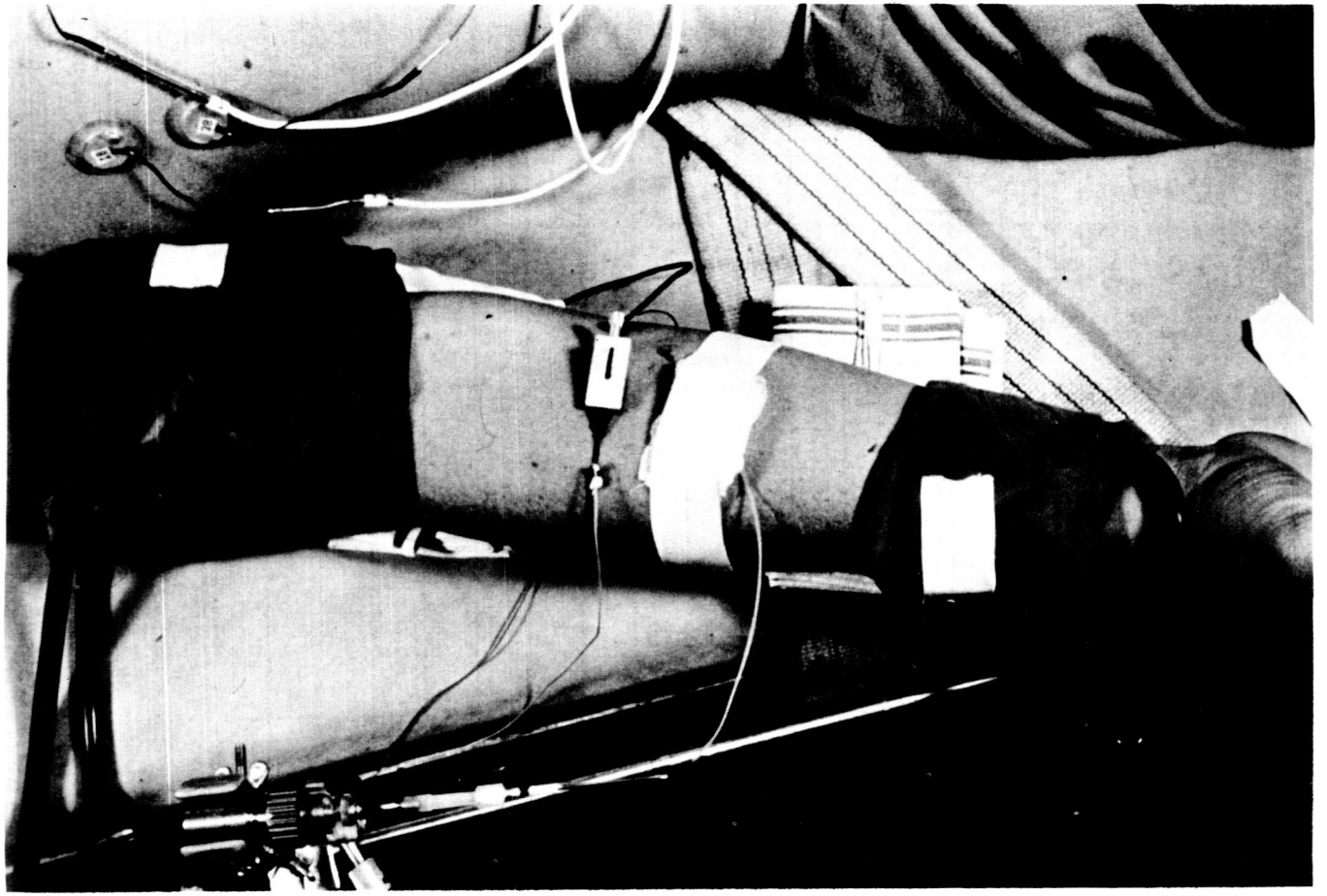

Figure 9.- Close-up views of system for obtaining forearm blood flow and venometor tone.

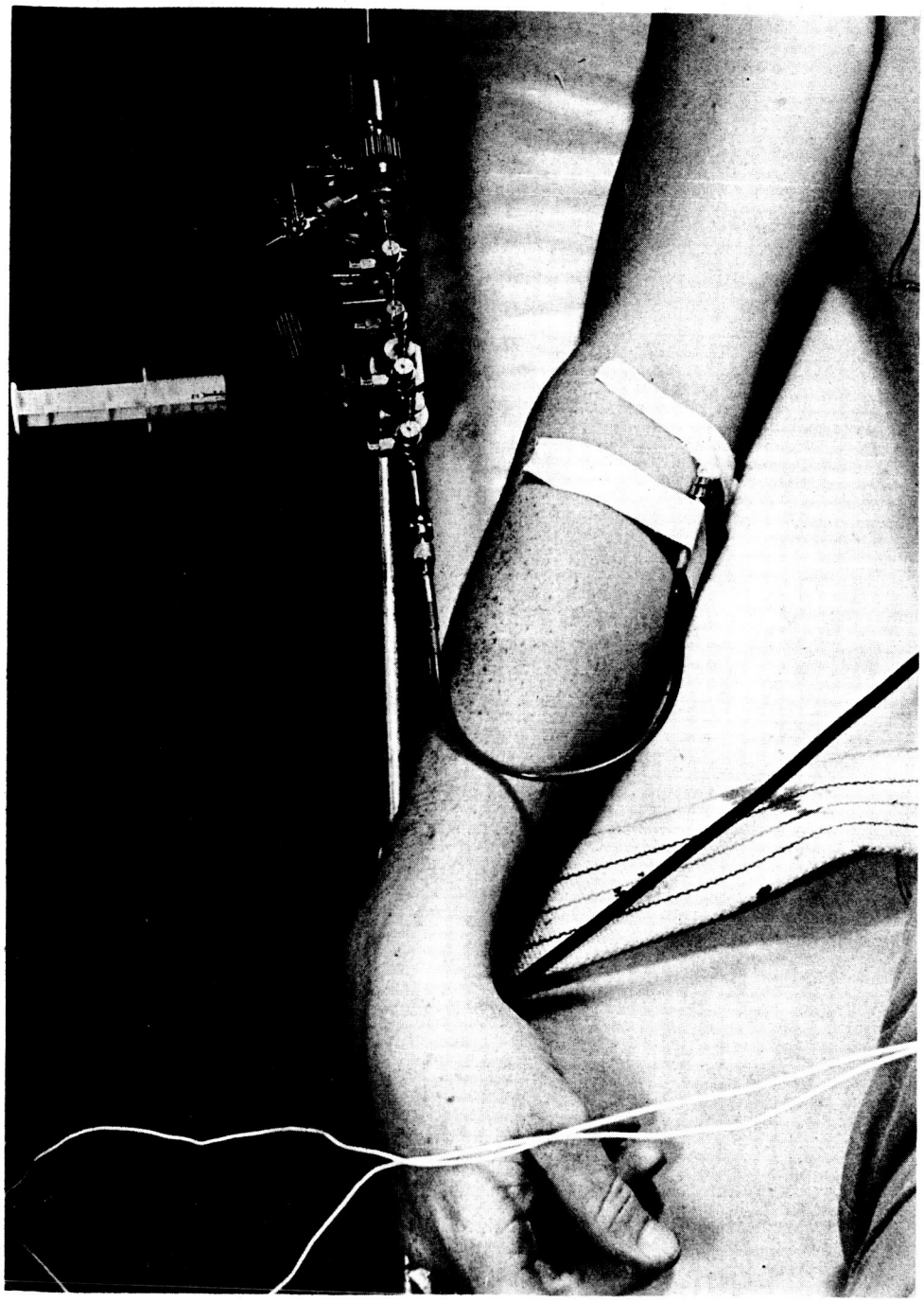

Figure 10.- Close-up of intra-arterial blood pressure measurement system.

10. Leg circumference measurements were made during the tilt-table tests by a mercury-in-rubber strain gauge placed around the calfs of both legs at the same site for each tilt procedure. Figure 11 shows a picture of the mercury-in-rubber strain gauge connected by wire to a Parks electronics amplifier not shown in the photograph. A calibrating device is attached in series with the strain gauge to provide a means of putting a calibrated change in circumference upon the strain gauge while it is in position of use. The device consists of a calibrating screw that can be adjusted to provide from 0 to 1 centimeter change in the circumference, with each turn of the screw providing a change in circumference of the strain gauge equal to the thread width of the screw.

Figure 12 shows a picture of the Flack device which consists of a whistle-type apparatus with a spring loaded piston to provide a 40 mm pressure load to expiration. Coming from the device is a small tubing which can be connected to a pressure transducer to allow for measurement of the intra-oral pressure. The device has a small air leak in back of the piston to prevent use of only the cheek muscles to obtain an intra-oral pressure of 40 mm Hg.

Figure 13 shows a sample record of the ECG, heart rate, intra-oral pressure and intra-arterial blood pressure obtained during a Flack procedure. At the bottom of the figure is a demonstration of the time code that is displayed on the strip-chart recorder. Figure 14 shows a sample of the type of data collected during a tilt procedure when the subject experiences syncope. At the time of tilt the heart rate increases and the blood pressure begins to show oscillations, with a general downward trend on the blood pressure and a distinct narrowing of the pulse pressure; also indicated in an increased respiratory activity.

DATA PROCESSING

The techniques of data processing utilized in this study have been selected as the most convenient to manipulate large volumes of multi-channel analog data that must be processed through the coordination of a number of groups of people. The data collected in 1964 provided approximately 300 hours of multi-channel analog data that came from repeated tilt-test procedures, Erkin exercises, and bicycle ergometry tests that occurred over a 3-month period on the same group of subjects. The achievements in data processing have resulted from the combined work on the principal investigators of the study, computer programing personnel located within the Texas Institute for Rehabilitation and Research, consultation and services from the Baylor University College of Medicine Biomathematics Department and computer facility, consultation from the Texas A & M Biostatistics group, digitizing effort of the IESD at NASA,

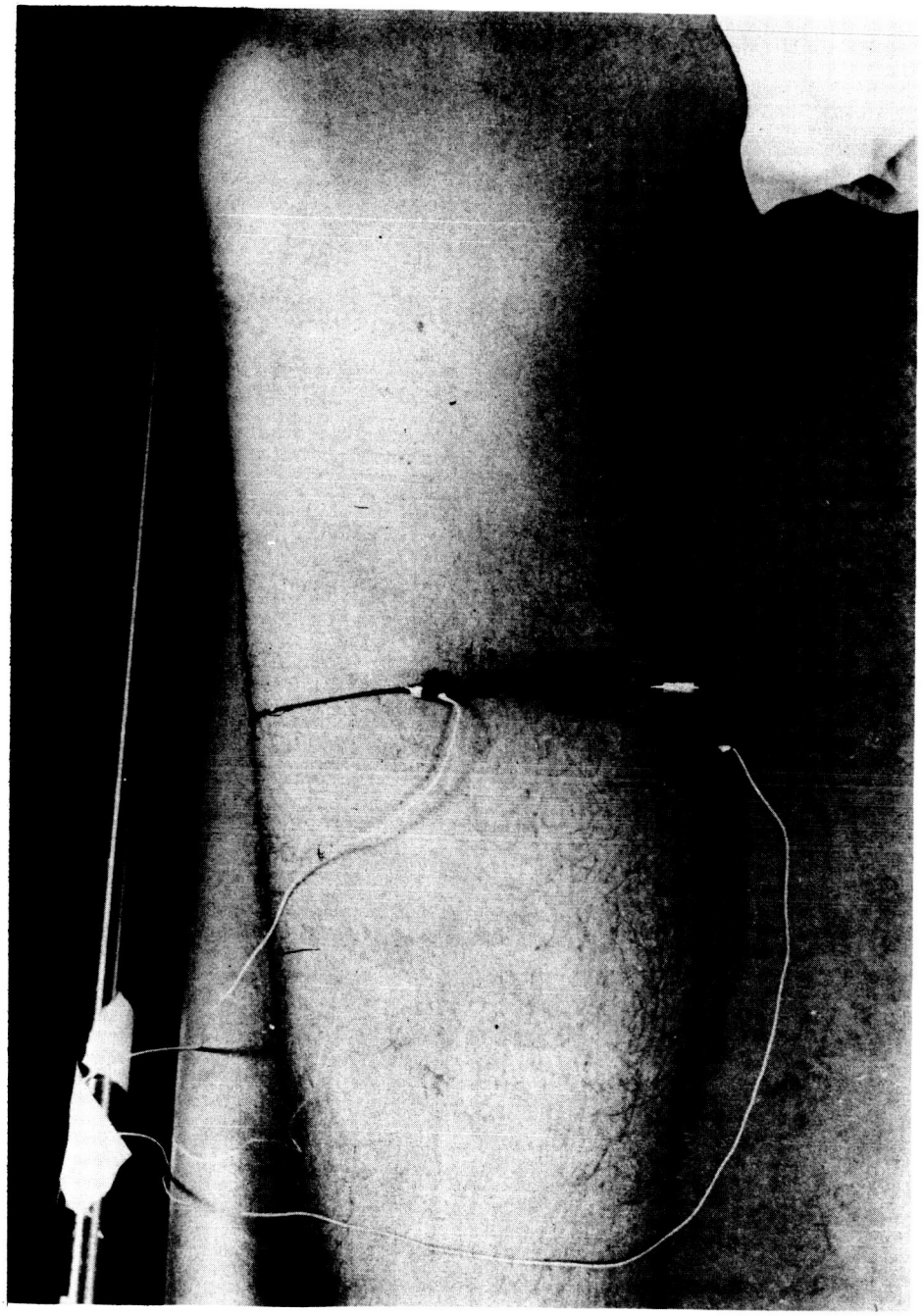

Figure 11.- Mercury-in-rubber strain gage for leg circumference measurements.

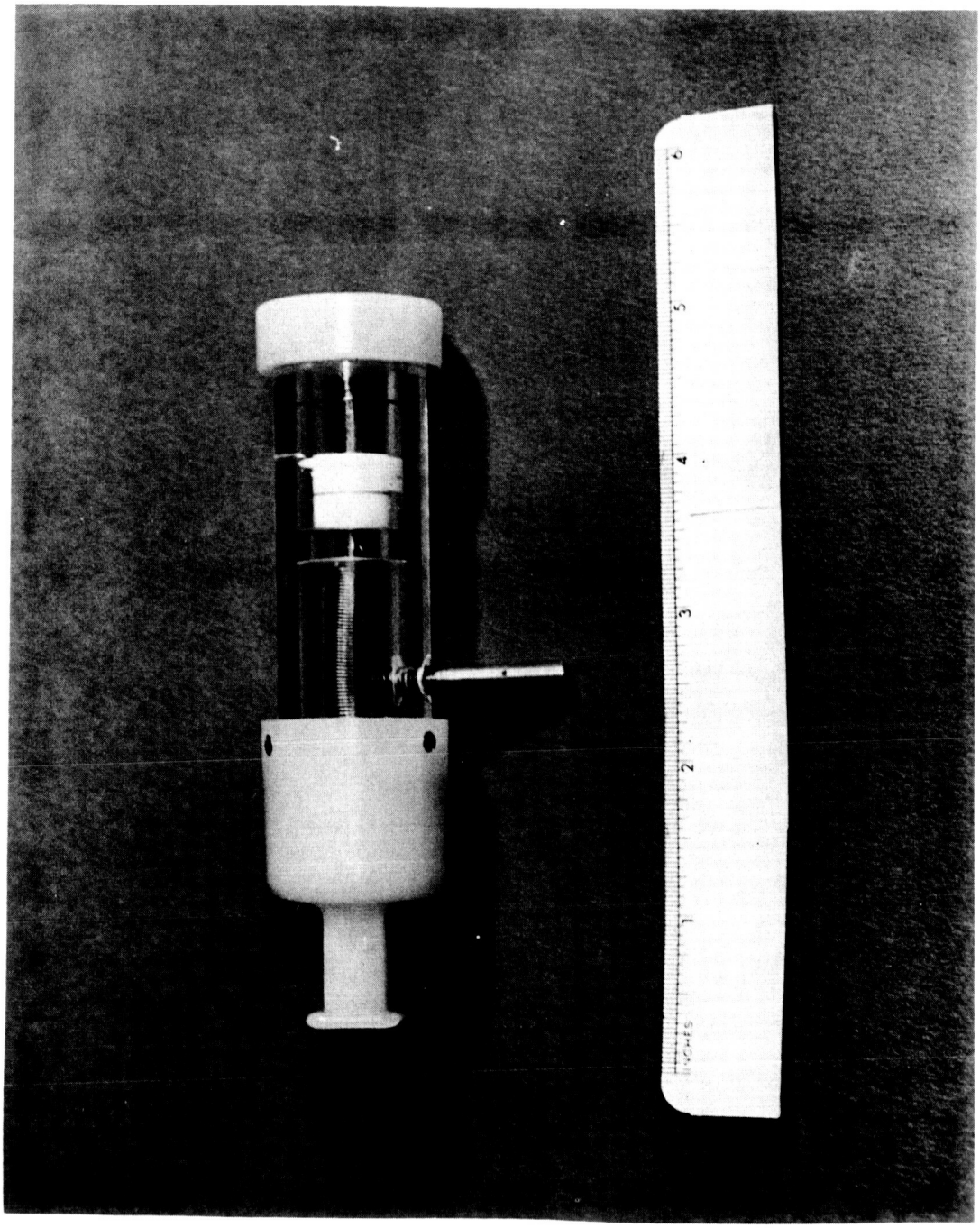

Figure 12.- Flack tester.

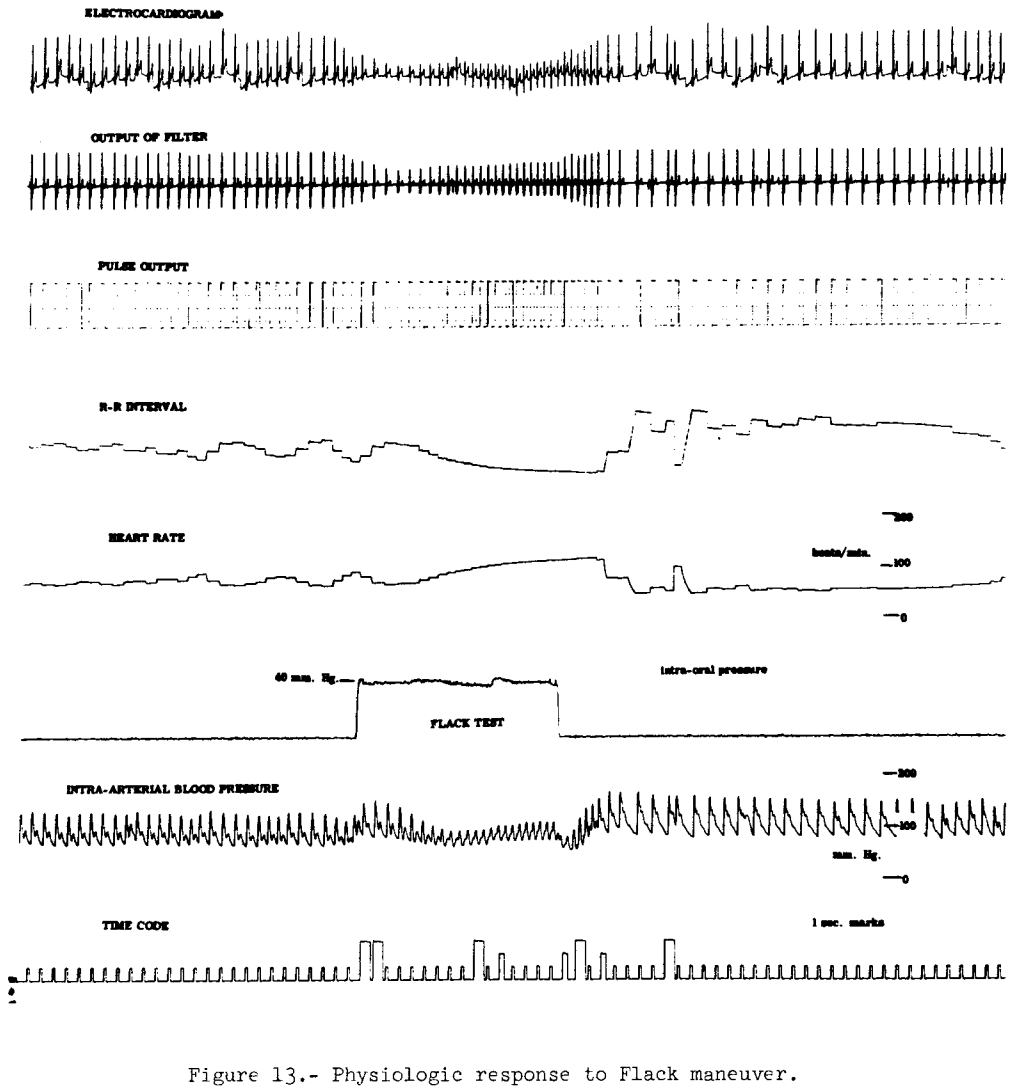

Figure 13.- Physiologic response to Flack maneuver.

Figure 14.- Tilt response after bedrest resulting in syncope.

programing from the Data Systems Branch of NASA, instrumentation from the Bioinstrumentation Section of NASA, and overall coordination from the Space Medicine Branch of NASA.

The data collected on the magnetic tape recorder or strip-chart recorder were basically of an analog type. For ease of manipulation, and for use on the computers to which access was available, it was necessary to convert the analog data into digital form. Two basic approaches were available for this conversion of data from analog to digital form: (a) a semi-automatic technique using a Telecordex as shown in figure 15, or (b) the Microsadic shown in figure 16. The Telecordex was available for use within the Texas Institute for Rehabilitation and Research, while the Microsadic was available only at NASA.

Because the Microsadic was available only at NASA and was operated by personnel unfamiliar with the basic experimental design or type of research, it became necessary to provide data description forms and digitizing request forms that could be used by the technical personnel who operated the equipment at NASA. Figure 17 shows an analog tape description form that is filled out at the time of recording data to identify the type of tape recorder, recording speed, and information on the various channels to completely categorize and identify the data. Figure 18 shows a data description form which is used for requesting digitizing of data from the group who operate the Microsadic digitizer. This same form also provides information describing the subject, the particular tests and measurements being made, the month, day, year, hour, and minute of the time of recording, and a start-stop time for digitizing. Both the start time and the stop time corresponded to the IRIG type B format recorded on the magnetic tape recorder. For convenience of separating data, an End of File mark is inserted on the digitized tape.

Figure 19 shows a detailed request to the Microsadic digitizer indicating sample rates to be used, scans per record, density on tape, channel constants, and the patching for input to the Microsadic. While some of this information is available at NASA, it was found that a clear understanding of the operation of all steps of the procedure from the Texas Institute for Rehabilitation and Research and a written request form with the total information would minimize the number of errors made and would save time on rerunning data. Figure 20 shows one view of the computer facility available at NASA, which consists of an IBM 7094 system.

Figure 21 shows an example of two basic types of measurements made during a tilt procedure. The data indicated in figure 21 shows samples of an electrocardiogram and intra-arterial blood pressure obtained from a subject during a tilt procedure. Both of these measurements are important indicators of cardiovascular instability which occurs when the subject is tilted to the upright position after prolonged periods of

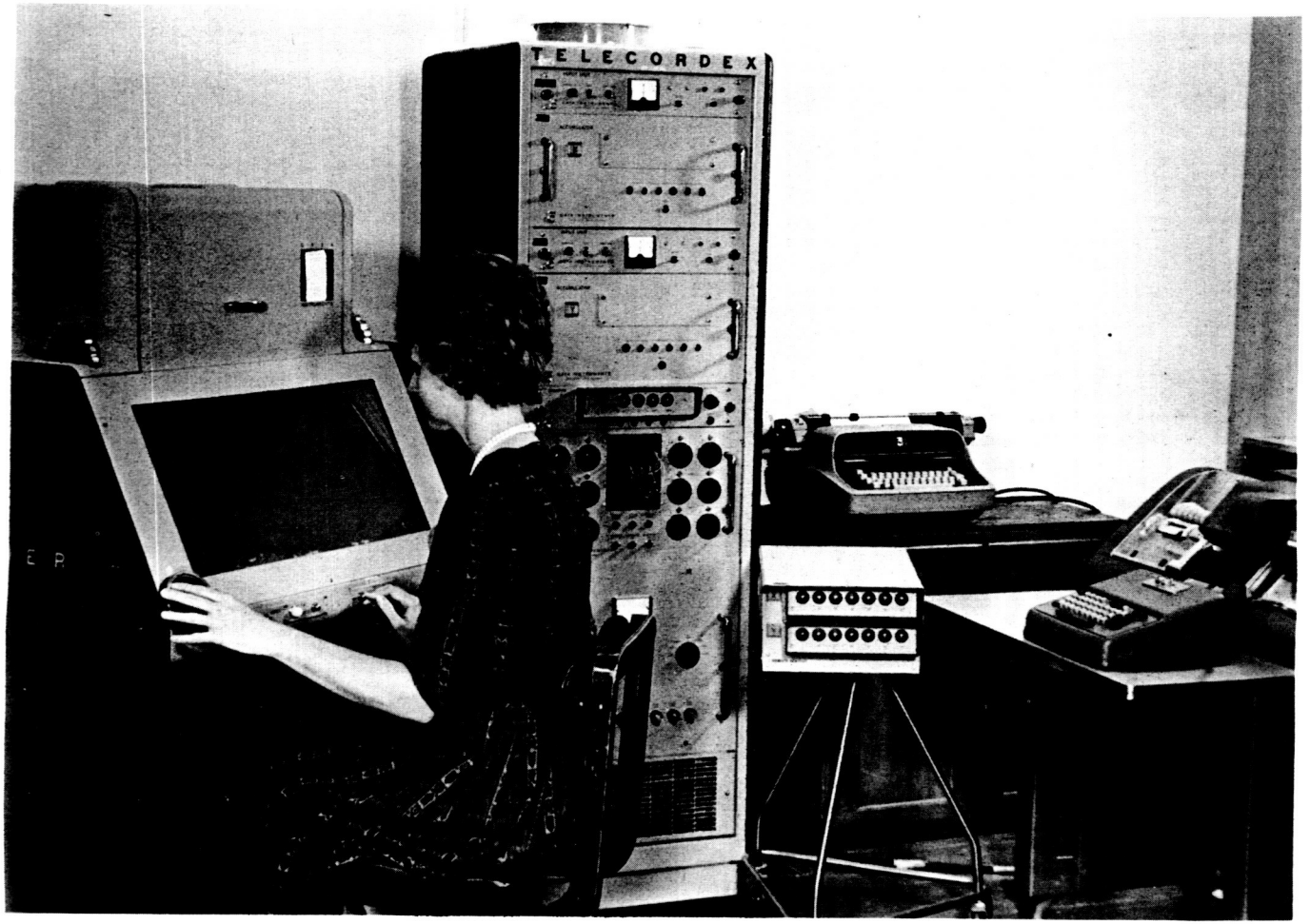

Figure 15.- Telecordex semi-automatic analog-to-digital computer.

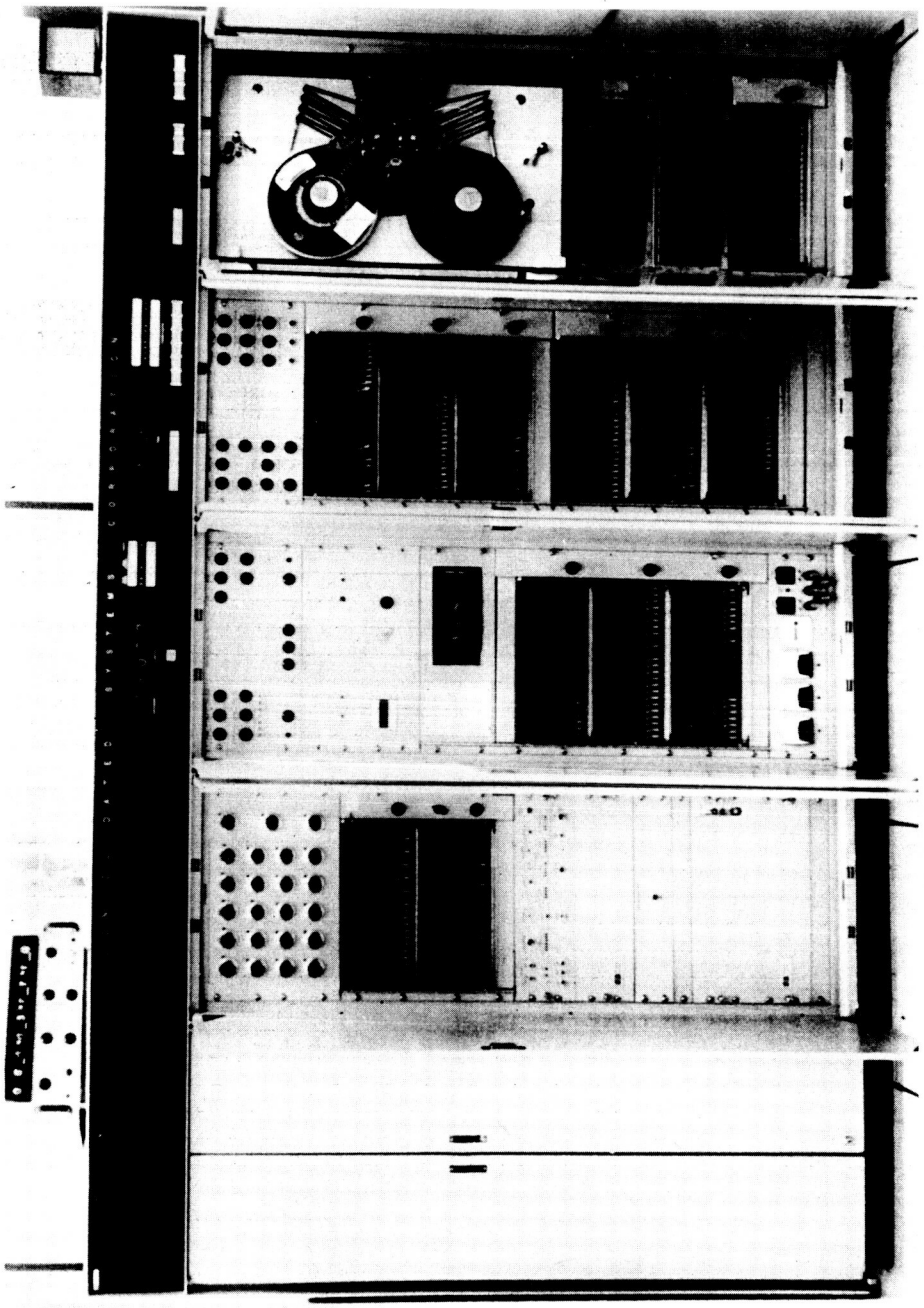

Figure 16.- Microsadic automatic analog to digital computer.

ANALOG TAPE DESCRIPTION FORM Page _____

SUBMITTER	DATE RECORDED	DATE SUBMITTED	DATE DIGITIZED

TAPE NUMBER	PROPERTY OF

RECORDING SPEED	C F U	RECORDING HEAD

TAPE TRACK	FUNCTION RECORDED	MEASUREMENT CODE
01		
02		
03		
04		
05		
06		
07		
08		
09		
10		
11		
12		
13		
14		
15		
16		
SIDE TRACKS		

Figure 17.- Analog tape description form.

DATA DESCRIPTION FORM

Page ____

Digital Tape Label						DeGauss						
Date Recorded					Tape No.	Start Approx. Footage						
Subject	General Study	General Phase	Specific Test	Specific Phase	Measurements	Date M	Date D	Date Y	Time H	Time M	Sequence	Start / Stop
												E.O.F.
												E.O.F.
												E.O.F.
												E.O.F.
												E.O.F.
												E.O.F.
												E.O.F.
												E.O.F.
												E.O.F.
												E.O.F.
												E.O.F.
												E.O.F.

Figure 18.- Data description form for digitizing.

MICROSADIC REQUEST FORM

SUBMITTER	ANALOG TAPE NO.	PROPERTY OF
NO. OF FILES	START DECODER	REMARKS
	Ft. Audio	

TAPE SPEED	TAPE WIDTH	RECORDER HEAD				CONDITION	
		Wide Band	Stan-dard	Irig Std.	Ind. Std.	Re-wound	Not Re-wound

SAMPLING RATE (KSPS)	SCANS PER RECORD	DENSITY	NO. CHNLS. MICROSADIC

CHANNEL CONSTANTS

RATE	SCAN	CHANNELS	TAPE SEQUENCE	DIG. TAPE REEL	DENS.

TAPE TRACK	CHANNELS	TAPE TRACK	CHANNELS

EDGE TRACK

DIGITAL TAPES PRODUCED	ORDER	REEL NUMBER	ORDER	REEL NUMBER
REMARKS:	1		8	
	2		9	
	3		10	
	4		11	
	5		12	
	6		13	
	7		14	

Figure 19.- Microsadic request form.

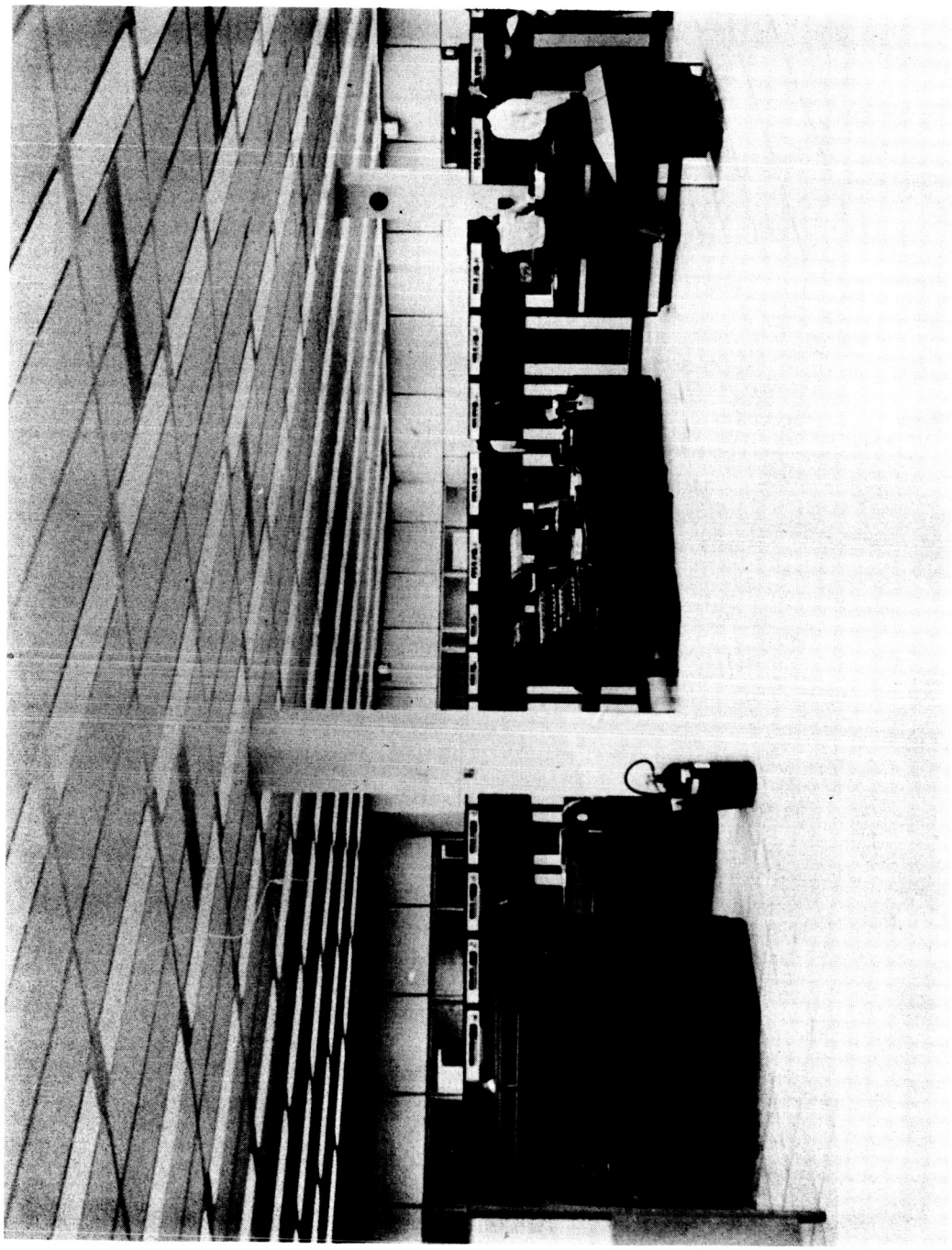

Figure 20.- View of NASA computing facility.

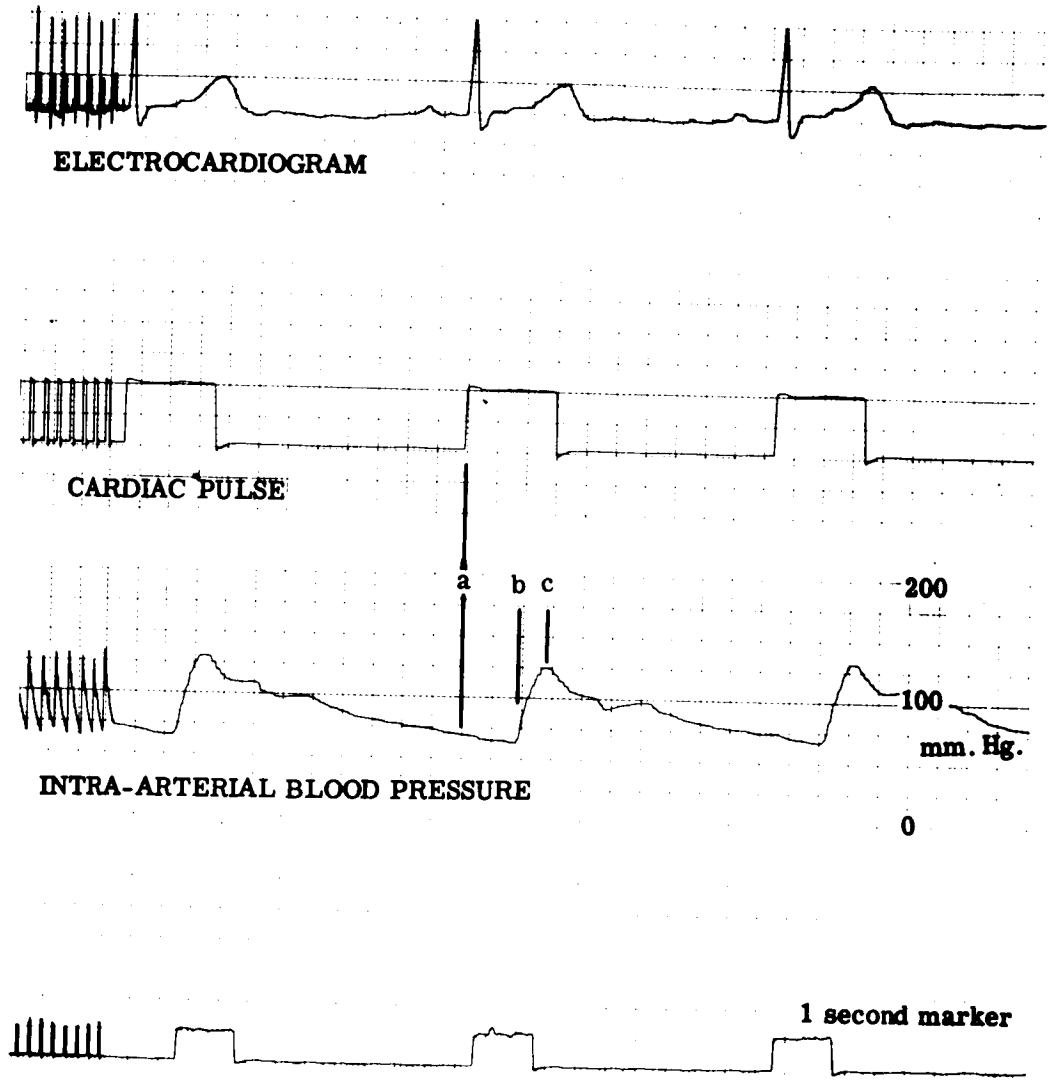

Figure 21.- Sample of data obtained during test indicating technique to identify digitizing data.

bedrest. The data shown in this diagram is of good quality and easy to read. However, in many cases (for example, during Erkin exercise or bicycle ergometry) the quality of data becomes poor due to interfering signals which at times tend to obscure the electrocardiogram. Also, computer recognition of the electrocardiogram due to baseline shifts, changes in QRS configuration or polarity, and false recognition of a T-wave for a QRS complex presents some difficulties in providing a simple means to obtain heart rate and blood pressure data. For this reason, a special electrocardiogram preprocessing unit which provided a single type of output for each cardiac cycle, regardless of the interfering signal or the configuration of the electrocardiogram, provided a means for easy recognition of each cardiac cycle. This cardiac pulse output is shown in the second channel of figure 21. Thus, after digitizing of the pulse output shown in the second channel of figure 21, there was required only a computer program to recognize a rapid change from a baseline to a positive value. Then, by searching another channel of digitized data, representative of the intra-arterial blood pressure in channel 3 of figure 21, a simple computer program was devised to determine the arithmetic minimum that occurs between points a and b, which thus indicate the diastolic blood pressure. Then by searching the same channel for a maximum within a prescribed period of time, it is possible to determine the systolic blood pressure indicated by point c in the diagram. Channel 4 of this figure shows the 1-second BCD code markers that are used for the identification of data on the strip chart recorders. There is a correspondence of the timing of this second marker and that obtained from the IRIG type B format code which is used for starting and stopping the digitizer; thus, there is a convenient means for editing of the data from the analog charts.

Figure 22 shows a sample of the computer output during a tilt procedure while the subject was in the horizontal position and shows the beat-by-beat heart rate calculated from the R-R interval, the diastolic blood pressure, and the systolic blood pressure. The time of occurrence of each of these events is indicated under Microsadic Time and corresponds to the actual experimental time recorded on the tilt-table code sheets. The location of the data on tape is indicated under the record, sample, and file title. In the lower portion of the record, there is indicated that occurrence of a zero, or opening of the blood pressure gauge to the atmosphere. This beat-by-beat indication of the tilt data is obviously more than would be desirable for interpretation of the large volume of data collected in these studies. Figure 23 shows a summary of data collected during a tilt-table test.

Figure 24 shows another means of displaying and summarizing data in the form of a graph to indicate trends of change. Indicated in this figure are the blood pressures, including systolic, diastolic and a calculated mean pressure during a tilt procedure. Five minutes of data is

HEART RATE	MICROSADIC TIME	RECORD	SAMPLE	DIASTOLIC PRESSURE	MICROSADIC TIME	RECORD	SAMPLE	SYSTOLIC PRESSURE	MICROSADIC TIME	RECORD	SAMPLE	FILE
63.16	0 58 5.040	1160	150	72.00	0 58 5.233	1162	23	121.39	0 58 5.355	1162	145	3
65.08	0 58 5.962	1166	112	73.41	0 58 6.121	1167	121	123.58	0 58 6.251	1168	91	3
65.50	0 58 6.868	1172	68	74.81	0 58 7.017	1173	57	123.97	0 58 7.175	1174	55	3
65.79	0 58 7.770	1178	20	74.03	0 58 7.973	1179	63	121.39	0 58 8.079	1180	9	3
66.37	0 58 8.674	1183	124	76.77	0 58 8.811	1184	111	124.05	0 58 8.975	1185	115	3
65.93	0 58 9.574	1189	74	77.94	0 58 9.717	1190	57	128.73	0 58 9.873	1191	53	3
64.38	0 58 10.496	1195	46	79.03	0 58 10.641	1196	31	128.03	0 58 10.803	1197	33	3
61.65	0 58 11.470	1201	60	76.53	0 58 11.647	1202	77	126.23	0 58 11.767	1203	47	3
62.24	0 58 12.424	1207	64	75.99	0 58 12.577	1208	57	129.52	0 58 12.731	1209	51	3
59.17	0 58 13.428	1213	118	75.28	0 58 13.589	1214	119	128.58	0 58 13.737	1215	107	3
61.35	0 58 14.406	1219	136	70.36	0 58 14.595	1221	15	120.92	0 58 14.707	1221	127	3
64.24	0 58 15.330	1225	110	71.77	0 58 15.511	1226	131	120.29	0 58 15.641	1227	101	3
66.37	0 58 16.224	1231	54	71.22	0 58 16.425	1232	95	120.92	0 58 16.527	1233	37	3
68.97	0 58 17.094	1236	124	73.22	0 58 17.289	1237	159	119.67	0 58 17.409	1238	119	3
71.77	0 58 17.920	1241	160	76.30	0 58 18.109	1243	29	117.72	0 58 18.241	1244	1	3
73.89	0 58 18.732	1247	12	78.49	0 58 18.739	1247	19	103.65	0 58 18.979	1248	109	3
73.80	0 58 19.534	1252	24	82.39	0 58 19.727	1253	57	126.23	0 58 19.847	1254	17	3
73.17	0 58 20.344	1257	44	80.67	0 58 20.539	1258	79	125.30	0 58 20.653	1259	33	3
71.09	0 58 21.188	1262	88	80.52	0 58 21.387	1263	127	127.02	0 58 21.509	1264	89	3
69.28	0 58 22.044	1267	154	80.91	0 58 22.241	1269	31	130.92	0 58 22.347	1269	137	3
66.37	0 58 22.948	1273	98	79.97	0 58 23.131	1274	121	129.91	0 58 23.235	1275	75	3
63.69	0 58 23.880	1279	80	73.88	0 58 24.079	1280	119	126.00	0 58 24.191	1281	71	3
68.34	0 58 24.748	1284	158	75.91	0 58 24.959	1286	49	123.26	0 58 25.055	1286	145	3
68.34	0 58 25.626	1290	76	73.72	0 58 25.805	1291	95	123.73	0 58 25.927	1292	57	3
70.09	0 58 26.472	1295	132	73.56	0 58 26.677	1297	17	121.55	0 58 26.783	1297	123	3
72.82	0 58 27.296	1300	156	74.66	0 58 27.471	1302	41	118.34	0 58 27.601	1302	151	3
74.67	0 58 28.096	1306	6	75.13	0 58 28.297	1307	47	121.78	0 58 28.401	1307	151	3
75.00	0 58 28.886	1311	6	77.00	0 58 29.091	1312	51	121.70	0 58 29.197	1312	157	3
74.44	0 58 29.692	1316	12	75.60	0 58 29.881	1317	41	119.67	0 58 30.001	1318	1	3
74.81	0 58 30.484	1321	14	78.10	0 58 30.685	1322	55	117.64	0 58 30.789	1322	159	3
74.07	0 58 31.294	1326	24	75.13	0 58 31.481	1327	51	124.05	0 58 31.595	1328	5	3
73.53	0 58 32.100	1331	40	0.	0 58 32.101	1331	41	0.	0 58 32.101	1331	41	3
70.26	0 58 32.954	1336	94	0.	0 58 32.955	1336	95	0.	0 58 32.955	1336	95	3
69.44	0 58 33.808	1341	158	0.	0 58 33.809	1341	159	0.	0 58 33.809	1341	159	3
71.94	0 58 34.632	1347	32	0.	0 58 34.633	1347	33	0.	0 58 34.633	1347	33	3
72.46	0 58 35.460	1352	60	0.	0 58 35.461	1352	61	0.	0 58 35.461	1352	61	3
72.64	0 58 36.276	1357	86	0.	0 58 36.277	1357	87	0.	0 58 36.277	1357	87	3
72.93	0 58 37.098	1362	108	0.	0 58 37.099	1362	109	0.	0 58 37.099	1362	109	3
72.27	0 58 37.918	1367	138	0.	0 58 37.919	1367	139	0.	0 58 37.919	1367	139	3
70.75	0 58 38.766	1373	26	0.	0 58 38.767	1373	27	0.	0 58 38.767	1373	27	3
68.49	0 58 39.632	1378	102	0.	0 58 39.633	1378	103	0.	0 58 39.633	1378	103	3
67.87	0 58 40.506	1384	26	0.	0 58 40.507	1384	27	0.	0 58 40.507	1384	27	3
68.49	0 58 41.382	1389	102	0.	0 58 41.383	1389	103	0.	0 58 41.383	1389	103	3
66.23	0 58 42.278	1395	48	90.60	0 58 42.497	1396	107	94.04	0 58 42.555	1397	5	3
66.23	0 58 43.174	1400	154	89.58	0 58 43.201	1401	21	94.12	0 58 43.291	1401	111	3
70.26	0 58 44.028	1406	48	0.	0 58 44.029	1406	49	0.	0 58 44.029	1406	49	3
71.43	0 58 44.858	1411	89	0.	0 58 44.859	1411	89	0.	0 58 44.859	1411	89	3
70.26	0 58 45.712	1416	142	73.17	0 58 45.875	1417	145	121.47	0 58 46.007	1418	117	3
66.96	0 58 46.598	1422	78	71.14	0 58 46.779	1423	99	120.29	0 58 46.903	1424	63	3
66.37	0 58 47.492	1428	22	71.69	0 58 47.689	1429	59	117.79	0 58 47.809	1430	19	3

Figure 22.- Computer output showing beat-by-beat readings of heart rate and blood pressure.

R TESCH | SUBJECT NO. 9 | 9-07-64 | TILT NO. 2 | COMPLEX TILT

TILT UP AT 6.0 MINUTES | SYNCOPE AT 18.5 MINUTES | TILT DOWN AT 19.0 MINUTES

TIME MIN	HEART RATE BEATS/MIN	SYSTOLIC B.P. MM HG	DIASTOLIC B.P. MM HG	PULSE PRESSURE MM HG	MEAN PRESSURE
1	64	117	67	50	83.67
2	62	115	65	50	81.67
3	64	110	60	50	76.67
4	64	122	70	52	87.33
5	63	114	65	49	81.33
6	88	108	70	38	82.67
7	96	112	73	39	86.00
8	103	98	58	40	71.33
9	101	110	70	40	83.33
10	101	100	58	42	72.00
11	104	111	70	41	83.67
12	103	97	58	39	71.00
13	103	98	58	40	71.33
14	104	109	63	46	78.33
15	104	97	58	39	71.00
16	113	98	60	38	72.67
17	94	113	53	60	73.00
18	70	75	50	25	58.33
19	60	129	80	49	96.33
20	61	134	82	52	99.33
21	59	130	74	56	92.67
22	58	132	75	57	94.00
23	63	120	68	52	85.33

AVERAGE HEART RATE PRE TILT	= 63.400	BEATS/MIN
MAXIMUM HEART RATE DURING TILT	=113	BEATS/MIN
MINIMUM HEART RATE AFTER TILT	= 58	BEATS/MIN
CHANGE IN HEART RATE WITH TILT	= 49.600	BEATS/MIN
FRACTIONAL INCREASE IN HEART RATE	= 0.782	
AVERAGE PRE TILT HEART RATE-AVERAGE POST TILT RATE	= 3.150	BEATS/MIN
TIME OF MAX HEART RATE FROM START OF TILT UP	= 10	MINUTES
TIME TO 80 PER CENT MAXIMUM HEART RATE	= 5	MINUTES
TIME TO PLATEAU	= 3	MINUTES
SLOPE TO 80 PER CENT HEART RATE	= 6.767	HEART RATE/MIN
SLOPE TO PLATEAU	= 9.400	HEART RATE/MIN
AVERAGE PULSE PRESSURE PRE TILT	= 50.200	MM HG
MINIMUM PULSE PRESSURE DURING TILT	= 25	MM HG
AVERAGE PRE TILT PULSE PRESSURE-MIN DURING TILT	= 25.200	MM HG
FRACTIONAL DECREASE IN PULSE PRESSURE	= 0.502	
TIME OF MIN PULSE PRESSURE FROM START OF TILT UP	= 12	MINUTES
AVERAGE PRE TILT MEAN PRESSURE-MINIMUM DURING TILT	= 23.800	MM HG

Figure 23.- Summary sheet of tilt-table data.

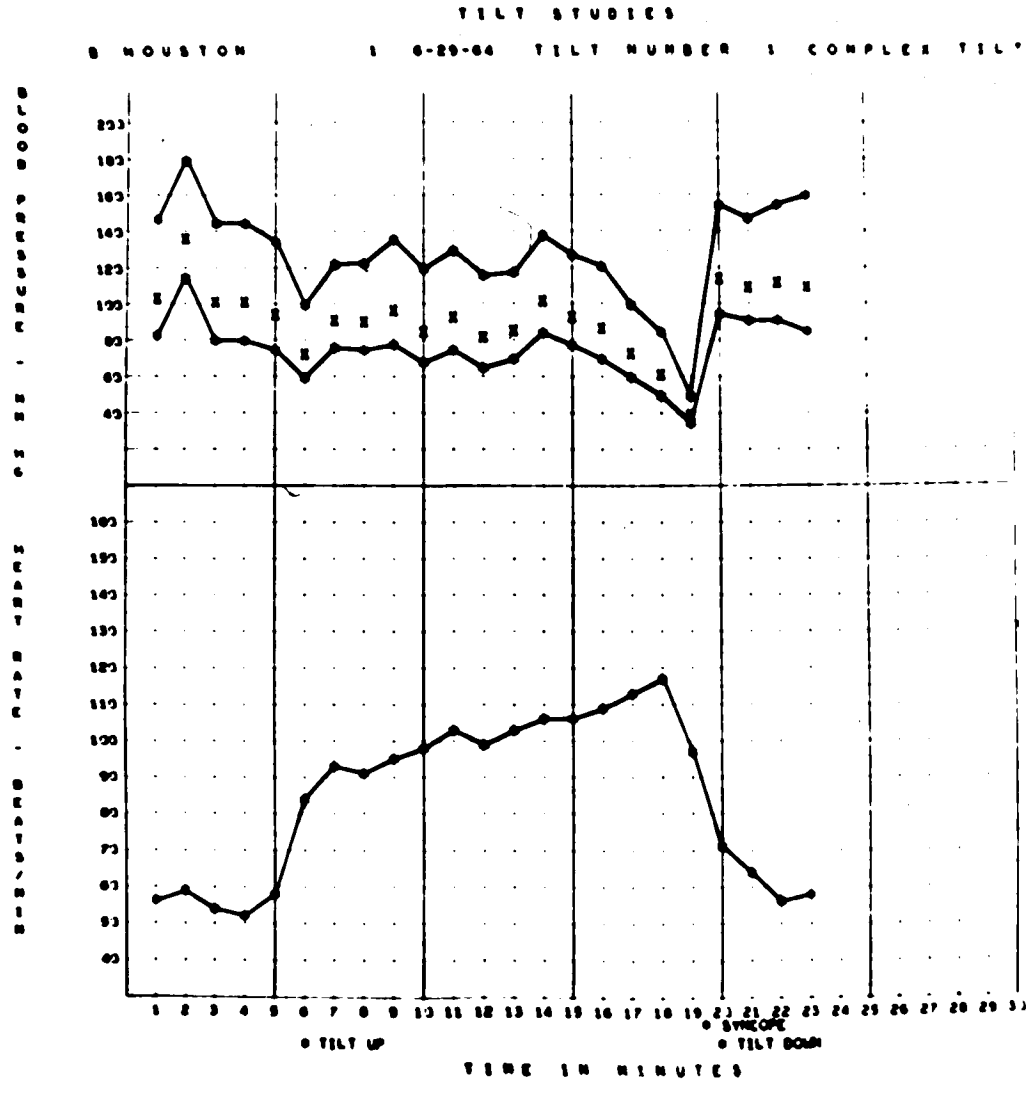

Figure 24.- Heart rate and blood pressure plot during tilt-table test.

shown prior to the tilt-up, and 5 minutes of data is shown after the occurrence of syncope. As shown from this graph, syncope occurred only minutes before the time the subject was due to be tilted down. The lower portion of the figure shows the change in heart rate that occurs in association with the changes in blood pressure noted above. The sample tilt shown here is from a subject after undergoing 10 days of bedrest.

The preceding information shows the techniques involved in reducing large volumes of data to a form that can be handled statistically, that can be displayed conveniently, and that can be retrieved for further analysis. The information given shows only the initial steps that have been made in developing techniques for the analysis and interpretation of the data acquired from the tilt procedure. The following several pages provide an example of a problem definition sheet that is compiled prior to the beginning of computer analysis. The attached sheet shows a sample of the steps that are made in the digitizing and display of data prior to statistical manipulation. Also indicated are some statistical procedures that will be applied to the data to determine the significance of the data for the test circumstances. There are other techniques of analysis and problem definition sheets involved for each of many phases of this project that follow the pattern of the one demonstrated. The information on the results of each of these studies and analysis techniques will be made available as they are compiled.

COMPUTER PROBLEM DEFINITION SHEET

TILT-TABLE STUDIES

Heart Rate and Blood Pressure Display and Analysis

A. General Information

Tilt-table tests are one of several tests which may be performed to evaluate the cardiovascular status of an individual. In an effort to define the cardiovascular deconditioning which occurs with prolonged bedrest and space flights, the tilt procedures have been incorporated into bedrest studies at the Texas Institute for Rehabilitation and Research. Changes in heart rate and blood pressure during the tilt procedure define certain known, and perhaps some undetermined aspects of the cardiovascular status of an individual. The purpose of the work defined herein is to summarize, display, and compute certain characteristics of the response to tilt in an effort to define better the changes that occur with bedrest and the effect of potentially preventive measures in controlling the deconditioning. It is a preliminary step in deciding the most appropriate studies which should be made using more advanced statistical techniques. One of the primary goals is to process and manipulate the total and voluminous heart rate and blood pressure data collected during a tilt procedure in an accurate and reliable manner.

B. Purpose

It is desired to determine a more exact meaning to the tilt-table test and the responses observed in order to:

1. Determine day-to-day variation in response of a given individual

2. Determine differences in response of different subjects in similar tests or treatment groups

3. Determine reproducibility of a tilt response (as manifested by syncope and other signs or symptoms) on a day by successive tilts for a given individual

4. Determine the meaning of a tilt response in defining cardiovascular deconditioning of bedrest and later space flight (Assume bedrest causes what we call cardiovascular deconditioning.)

5. Determine if a treatment technique lessens the degree of deconditioning shown in the tilt test

6. Determine if there is a conditioning effect to repeated testing by tilt procedures (that is, is last control test different from first or second control?)

7. Determine if intra-arterial blood pressure and complex measurement techniques produce different responses to that observed with a simplified tilt procedure

8. Ultimately correlate the tilt response as a measure of deconditioning to bicycle tests, Erkin tests, leg circumference changes vonomotor tone, fluid and electrolyte balance, and body compartment measurements to each other to define the most appropriate means to describe the cardiovascular deconditioning of bedrest, with a final goal to arrive at its mechanism and prevention or control

C. Method or Model to Follow

1. Perform preliminary analysis on hand-reduced data presented as card input.

   a. Card data defines heart rate, systolic blood pressure and diastolic blood pressure for minute intervals, time of syncope, and identification data

   b. Calculate pulse pressure by subtracting diastolic from systolic blood pressure (PP = S - D)

   c. Calculate mean blood pressure by the following equation
   $M = D + \frac{1}{3}(S - D)$

   d. Plot on baseline for discontinuity of data points.

   e. Template

      (1) Tables

         (a) Subject name
         (b) Subject experimental number
         (c) Date of tilt
         (d) Tilt number for a given date (maximum of 3)
         (e) Type of tilt
            (aa) Complex - intra-arterial needle, et cetera done pre- and post-bedrest
            (bb) Simple - all other than complex (just blood pressure and ECG)

(f) Time of tilt-up (all occur at 6 minutes)
(g) Time of syncope or no syncope
(h) Time of tilt-down
(i) For successive minutes, 1 through 30, unless syncope, indicate heart rate (beats/minute), systolic blood pressure (mm Hg), diastolic blood pressure (mm Hg), pulse pressure (mm Hg), and mean pressure (mm Hg)
(j) Tabulate
    (aa) Average heart rate pre-tilt (beats/minute) (Usually 5 minutes pre-tilt observation)
    (bb) Maximum 1 minute average heart rate during tilt (beats/minute)
    (cc) Change in heart rate with tilt (beats/minute) Maximum 1 minute average during tilt minus average pre-tilt
    (dd) Minimum heart rate (1 minute average), post-tilt (beat 1 minute)
    (ee) Fractional increase in heart rate during tilt
    (ff) Average pre-tilt heart rate minus average post-tilt heart rate (beats/minute)
    (gg) Time from start of tilt up to time of 1 minute average maximum heart rate (minutes)
    (hh) Time from start of tilt up to minute in which at least 80 percent of change in heart rate occurs (minutes)
    (ii) Time to "plateau" defined as occurring when 1 minute average heart rate is less than previous minute, and occurs after second minute of tilt (minutes)
    (jj) Slope to 80 percent heart rate. Use time = 0 as 5 minutes with a value of mean for previous 5 minutes (heart rate/minute)
    (kk) Average pulse pressure during tilt (mm Hg)
    (ll) Minimum pulse pressure during tilt (mm Hg)
    (mm) Average pre-tilt pulse pressure minus minimum during tilt (mm Hg)
    (nn) Fractional decrease in pulse pressure
    (oo) Time of minimum pulse pressure from start of tilt-up (minutes)
    (pp) Average pre-tilt mean pressure minus minimum during tilt (mm Hg)
    (qq) Average pre-tilt mean pressure minus minimum during tilt (mm Hg)
    (rr) Slope of linear regression curve for time of tilt-up plus 1 minute to tilt-down minus 1 minute

(ss) Express variation of blood pressure as residual sum of squares

(2) Graphs - size $8\frac{1}{2}$" by 11" pages

(a) Identification
(aa) Tilt studies
(bb) Subject name and experimental number
(cc) Date of tilt
(dd) Tilt number
(ee) Type of tilt

(b) Graph - pulse pressure and heart rate
(aa) Units - mm Hg, beats/minute
(bb) Indicate tilt-up and tilt-down, syncope
(cc) Pulse pressure range 30-120 mm Hg
(dd) Heart rate range 40-160 beats/minute

(c) Graph - blood pressure: systolic, diastolic, and mean
(aa) Units mm Hg, beats/minute
(bb) Indicate tilt-up, tilt-down, and syncope
(cc) Blood pressure range 40-200 mm Hg
(dd) Heart rate range 40-160 beats/minute

(3) Output cards - all derived summary information for use in future statistical analysis

(4) Make a duplicate copy of output for use by statistical, analyzers, contract monitor, et cetera

f. Perform statistical analysis to determine significant

(1) Perform a step-down multiple regression to examine relation of the various parameters

(2) Perform analysis of variance as will be defined later for each grouping of data

2. Perform a complete analysis of heart rate and intra-arterial data using automatic analog-to-digital processing to retain all data

a. Data was collected on analog tapes at the time of tilting

(1) A strip-chart recording of the input to the tape recorder is made simultaneously and can be used for editing

e. Calculate pulse pressure (mm Hg): Pulse pressure = systolic - diastolic

f. Data discrimination or editing. The program for automatic recognition of a heart beat or blood pressure does not provide for absolute data discrimination due to poor data, wrong data, stopped up needle, flushing of needle, electronic mean imposed on records, et cetera. Provisions should be made for the following flexible changes in absolute value for special case as more experience is gained

(1) Card input for editing of an individual's record
(2) Read around a file
(3) Occasional deletion of heart rate data
    (a) Omit rates less that 35/minute
    (b) Omit rates greater than 200/minute
(4) Blood pressure - omit if:
    (a) Systolic less than diastolic
    (b) Systolic less than 40 mm Hg
    (c) Diastolic less than 30 mm Hg
    (d) Systolic greater than 220 mm Hg
    (e) Diastolic greater than 120 mm Hg
    (f) Pulse pressure less than 15 mm Hg
    (g) If only a systolic or diastolic reading is obtained for a given heart beat
    (h) Read 1-7 as full scale
    (i) If a reading of -10 to +10 mm Hg is obtained, read it. This allows for verification of baseline

g. Flack data to be considered in future. Omit for present study. May want to digitize now, however

h. At time of tilt, blood pressure readings must be corrected to a standard reference point. Each tilt for each subject will have a different correction figure which must be subtracted from both systolic and diastolic blood pressure before calculations are made

i. Determine effect of first Flack procedure

(1) In pre-Flack period, of duration "n" minutes, determine mean and standard deviation for heart rate and blood pressure measurements
(2) For the two minutes immediately prior to tilt, do a mean and standard deviation of heart rate and blood pressure data

(3) Do a pooled T test between the sets of data in (1) and (2)

j. For tilt data, calculate a regression line (assume linear and test for residuals). Do analysis of variance - total, regression error -)

(1) Apply to first 30-second, 60-second, and 90-second periods
(2) Apply to entire tilt excluding first 30-second, 60-second, and 90-second periods
(3) Express in appropriate units
(4) Apply to heart rate, (RR interval ?), systolic blood pressure, mean blood pressure, diastolic blood pressure, pulse pressure

k. For data after tilt-down, do as in (j) except consider 30-second, 60-second, and 90-second periods for first regression calculation. Apply to next 4-5 minutes of data excluding first 10 seconds, 30 seconds, 60 seconds, 90 seconds of tilt-down. (Use 10 seconds, since some are tilted down rapidly if syncope recurs. All tilt-ups require 30 seconds on motorized table)

l. Determine exact form for requests for digitizing to give your desired files. Inform me as soon as possible so we can fill out request forms

m. The original analog tapes for the complex tilts will not follow an exact schedule and may be on a 2-hour period. From start of tilt to second Flack is a very exact procedure, however. The tilt is 20 minutes unless there is syncope, and the second Flack is usually very close to 5 minutes after tilt-down

n. Template - similar to hand-reduced data

D. Data Source

Analog tapes at TIRR for editing; digitizing at NASA building 15, IESD; digital tape at NASA computer facility for final tape. Keypunch sheets from hand-reduced data are available at TIRR

E. Volume of Data

1. Number of patients - 11 subjects

2. Amount of data - 11 subjects, 130 tilts, approximately 40 minutes each or approximately 120 hours of data. Sixty of 130 tilts have both ECG and BP data, the other 70 will automatically process only heart rate data

3. Time span of experiment - summer of 1964

4. Continuing study

F. Source of Funds

NASA Contract No. NAS-9-1461 for direct TIRR expenditures. Support of the NASA computer facility

G. Equipment

Recording and playback system at TIRR

H. People to coordinate with

1. Oscar - not applicable

2. Keypunch - for hand-reduced data on keypunch sheets

3. Magnetic tape playback - for playback to Offner for editing of analog data and putting on cardiac pulse for computer recognition

4. Programer - TIRR to coordinate with NASA for heart rate and blood pressure data

5. NASA digitizers - Microsadic

6. Plotters - NASA 4020

7. Other - Statistical help

THE EFFECT OF EXTREMITY CUFF-TOURNIQUETS ON TILT TABLE INTOLERANCE AFTER WATER IMMERSION

Fred B. Vogt, M.D.
Texas Institute for Rehabilitation and Research

Studies have been conducted that demonstrate cardiovascular deconditioning occurs with prolonged bedrest (refs. 20, 8, 30, 21, 5, 25, 22, 29, 6, and 18) water immersion, (refs. 10, 14, 15, 11, 12, 2, and 17) chair rest, (ref. 16) or space flight (refs. 4 and 7). The physiological changes that occur in these experimental conditions which are responsible for the increase in heart rate, decrease in blood pressure, and signs or symptoms of syncope during tilt-table tests are not clearly understood. The lack of knowledge on the mechanism of deterioration of the cardiovascular system thus has made research on preventive and control measures difficult.

Anti-gravity suits have been found beneficial (refs. 18 and 19) in preventing orthostatic cardiovascular intolerance in patients, as well as normal subjects deconditioned by either bedrest or water immersion. Periodic rocking beds (ref. 30) in a gravity environment have been reported to produce some protective effect from the deconditioning associated with bedrest. Intermittent occlusive venous cuffs have been reported (ref. 10) to prevent the occurrence of tilt intolerance after water immersion. The purpose of the work reported in this paper was to reproduce some of the observations made in the water immersion experiment (ref. 10) in which cuffs provided a protective effect.

METHODS

Four healthy adult male college students in the age range 21 to 25 years who had participated previously in extensive bedrest studies (ref. 24) were used as subjects. Table I summarizes the subject characteristics.

TABLE I.- SUBJECT CHARACTERISTICS

Subject initial	Age (years)	Weight (kg)	Height (cm)	B. S. A.* (m^2)	Student occupation
C. E. R.	25	84.4	192.4	2.15	Student athlete
R. S. H.	22	66.5	172.4	1.80	Student athlete
W. F. M.	23	67.5	171.0	1.81	Dental student
B. E. H.	21	70.2	177.8	1.88	Student

*From Dubois Body Surface Chart by Boothby and Sandiford

The subjects underwent two 6-hour periods of water immersion, preceeded and followed by a tilt-table test. During the periods of water immersion, the subjects were dressed in bathing trunks and were immersed in a head-out position. They were allowed a minimum amount of activity in the pool, but most of the time remained in a sitting position. Accessory breathing apparatus was not used. The temperature of the water was maintained at approximately 93° F throughout the periods of immersion.

The day following test number one, the subjects underwent a second period of immersion, test number two, during which they had cuff-tourniquets applied to all four extremities. The cuffs were $3\frac{3}{4}$-inches wide and were held in place by a Velcro material. Because of the posture the subjects maintained during immersion, the cuffs on the lower extremities were located approximately 60 to 70 centimeters beneath the surface of the water. The cuffs were inflated from a pressure bottle air source to a pressure of 60 millimeters of mercury, with a 1-minute-on, and 1-minute-off time cycle, and had an inflate and deflate period of approximately 5 seconds. Cuffs on all subjects were inflated simultaneously.

A tilt-table test was performed during and after the water immersion periods using a tilt table with an English saddle type of support described elsewhere (ref. 26). The tilt table was motorized and tilted from horizontal to 70° in 30 seconds. With syncope, or impending syncope, the gear mechanism of the table was disengaged and the subject was tilted down immediately. The subject was transported from the immersion tank to the tilt-table test area by means of a stretcher and immediately went into the tilt-table test.

The electrocardiogram, impedance pneumogram, cuff-microphone blood pressure, and leg circumference changes were measured during the tilt test using an instrumentation system described elsewhere (ref. 28). The impedance pneumogram and electrocardiogram were taken from electrodes placed across the thorax in the fifth or sixth intercostal space. Indirect blood pressure apparatus (ref. 9) was attached to the right arm with a crystal microphone located over the brachial artery; the cuff was operated in 30-second cycles. Leg circumference measurements were made using a Whitney (ref. 31) mercury-in-rubber strain gauge apparatus applied to the calf of each leg. A 5-minute baseline recording was obtained prior to a 20-minute tilt to the 70° position. A 5-minute period of recording then was obtained after return of the subject to the horizontal position.

The subjects were immersed from 13:00 to 19:00 o'clock to correspond to a urine collection period that was used for a previous 90-day study (ref. 24) on this group of subjects. During the periods of immersion,

intake and output were carefully recorded. Weights were obtained prior to and after immersion. The subjects were allowed to drink fluid ad libitum. They were fed after the tilt procedure which immediately preceeded the immersion period, and this intake was included as part of their over-all intake. A malted milk was given to them after approximately 4 hours of immersion.

RESULTS

All four subjects showed a normal response to the control tilt prior to water immersion which was comparable with the responses observed in extensive tilt studies performed on them previously over a period of several months. There was noted an increase in heart rate and a slight rise in the diastolic blood pressure and a slight decrease in the systolic blood pressure, with a distinct narrowing of pulse pressure. There was no definite downward trend of systolic or diastolic blood pressure. There were no definite downrange trends of systolic or diastolic blood pressure. There were no signs of symptoms of impending syncope during the control tilt-table procedure.

Three of the four subjects showed syncopal reactions following the first 6-hour period of water immersion. Figure 1 summarizes the duration of tilt procedure by bar graphs. The change from a pre-tilt 5-minute average heart rate to the maximum 1-minute average heart rate during tilt for the subjects is shown by a darkened bar line in the center of the bar representing duration of tilting. The third subject, C. E. R., did not show syncope, but did demonstrate a significant rise in heart rate in his first post-immersion tilt test.

During the tilt test following the second water immersion period, to which a cuff-tourniquet treatment had been added, none of the four subjects experienced synocope. There was evidence of an increase in heart rate which was not as great as that after the first test.

Figures 2, 3, 4, and 5 show the tilt-table data in graphic form for each individual to allow ready comparison of the responses for the various test circumstances. Dashed lines represent control values and solid lines the post-immersion values. Five minutes of control data is presented prior to tilting to 70° and 5 minutes of recovery data is presented after tilt down.

Subject weights did not change significantly during the immersion periods and the minor changes are accounted for by the intake-output differences during the test. None of the subjects complained of excessive thirst at any time. Table II presents the changes in body weight, oral intake, and urine output data obtained during the two tests. There appeared to be some difference in the volume outputs for the two immersion periods, but the urine specific gravity did not change significantly during the period of immersion. Total urine volumes were somewhat higher than the average volume outputs for corresponding timed periods of collection in studies performed previously on the subjects, but the range in day-to-day variation in these earlier studies is large

enough to make it impossible to say that a significant diuresis existed during this water immersion study.

Leg calf measurements made in the recumbent position on the tilt table prior to tilt did not show significant changes post-immersion compared to pre-immersion. Calf circumference changes during tilt ranged from 3 to 5 percent during the 20-minute tilt, but there was no good correlation of this with the degree of tilt-table intolerance observed.

DISCUSSION

The mechanism of the protective effect of the cuff-tourniquets suggested in Graveline's experiment (ref. 10) and reproduced to some extent in this study is not clear. Interpretation of the effects becomes difficult because of the many complicating factors that result from placing a person in a warm and wet environment, and one which provides pressure forces that act upon the body cavities in a poorly understood manner. Of significance, however, is that the tilt-table intolerance does occur with water immersion in as relatively a short time span as has been found in space flights, and that it is prevented under experimental conditions identical to that which produces the deconditioning except for the addition of extremity cuff-tourniquets. Of even more significance is that this type of treatment or preventive technique offers itself to application to space flight situations since its mechanism of operation does not depend on a gravity environment. However, the likelihood of protection from cardiovascular deconditioning of space flight by a similar cuff-tourniquet technique would likely depend on a common mechanism of production to that found with water immersion. A possible mechanism to explain some of the factors responsible for the tilt-table intolerance seen after water immersion is discussed elsewhere (ref. 27) in observations made on the same group of subjects who participated in the study reported herein.

The use of subjects in this experiment who have had considerable experience with tilt-test procedures lessens the likelihood of any sporadic subject responses because of extreme anxiety or uncertainties of experimental procedures on the part of the subjects. Further, since the two experiments were performed in close time relationship, any bias due to lack of reconditioning of the subjects would be against reproducing the findings of Graveline (ref. 10).

Diuretic responses have been known to occur with prolonged water immerson. Bazett (ref. 1) noted this diuresis as early as 1924 and numerous other observers, (refs. 14, 11, 12, 2, and 13) have confirmed it. One group (ref. 3), however, did not report a diuresis with water

immersion. The failure to observe a significant diuresis in this study raises further questions as to the meaning of diuresis observed by others. But, the failure to observe a marked diuresis and intense thirst, while at the same time observing considerable signs of cardiovascular deconditioning points to this diuresis being a less significant contributing factor to the tilt intolerance. Consideration must be given to the fact that these subjects previously had undergone many test procedures in the experimental laboratory. Anxiety in an inexperienced subject could result in a chain-reaction of increased-intake, increased-output to explain some of the observations in other studies. It is also possible that this group of subjects may have experienced a diuretic response if they had been immersed for a longer period of time. A more detailed account of the fluid-electrolyte and plasma volume responses found in this experiment is in progress and will be reported at a near date (ref. 27).

Cardiovascular deconditioning is spoken of in terms of the orthostatic increase in heart rate, drop in blood pressure, and signs and symptoms of impending or actual syncope. From the experience of the author, it would seem that the order of severity of tilt intolerance after prolonged bedrest is reflected first in heart rate changes, next by narrowing of pulse pressure with a trend downward in blood pressure, with systolic pressure falling predominantly until the presyncopal condition presents, and then finally, syncope. It has been noted (ref. 23) that in the final minutes before syncope, the beat-by-beat variation in heart rate became minimized and the heart rate decreased at the same time that the blood pressure decreased. This parallel drop of heart rate and blood pressure is different from the out-of-phase relationship seen when the subject compensates to the upright position. The responses to tilting after water immersion seem comparable to those observed after bedrest, although they may be produced by much shorter exposure to the experimental deconditioning test.

A point that deserves more consideration in evaluating the protective effect of cuff-tourniquets in this experiment is raised because of counteracting effects produced because of varying depths of the cuffs below water level. In this experiment, a 60-millimeter mercury pressure referenced to the atmosphere was applied to all cuffs. The effect of this pressure in producing additional constriction to the lower extremities above that resulting from the weight of the water itself is the force difference of the pressure applied to the cuff and the pressure force produced by the weight of the water. The implication in this experiment is that perhaps more of the "treatment effect" resulted from the cuffs on the upper extremities.

The simplicity of this experiment and the complexity of the changes in physiological mechanisms with water immersion raise as many questions as are answered. Still, there have been shown to be some protective

effect from the use of the cuff-tourniquets. The continued observance of marked changes in heart rate after immersion when cuffs are used indicates that only a first step has been made in the control of the tilt-table intolerance after water immersion. Further, there is still no evidence that the cardiovascular deconditioning of water immersion is the same as that found with bedrest studies or in association with orbital flight. Strong considerations and considerable emphasis should be placed on developing "control mechanisms" to protect against the hazardous effects of cardiovascular deconditioning of space flight until more is known of the true meaning of the deconditioning and adequate "preventive measures" can be developed. Continued intensive and cooperative efforts of all investigators in these research areas must be directed to meeting both of these requirements if we are to meet our responsibilities of not only studying the effect of space on man, but in protecting him from these effects.

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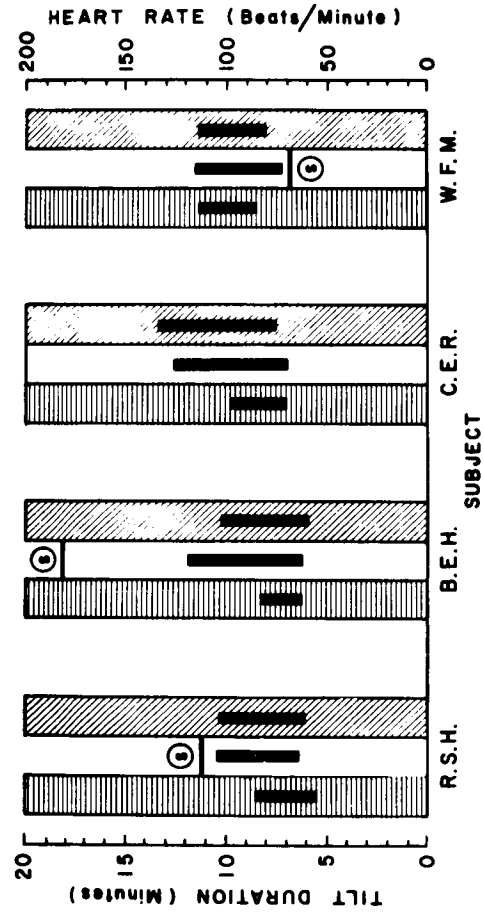


Figure 1. Summary of tilt characteristics for water immersion subjects.

The height of the first bar for each subject represents the tilt duration for the control tilt; the height of the second bar represents the tilt duration for the tilt following 6 hours of water immersion; and the height of the third bar represents the tilt duration for the water immersion experiment to which extremity cuffs were added. The occurrence of syncope is represented by (S). The solid lines in the bar graphs represent the change in heart rate from a pre-tilt five minute average to the maximum one minute average in the 70° position.

TABLE II.- ORAL INTAKE - URINE OUTPUT DURING WATER IMMERSION

		Test number 1			Test number 2		
Subject	Control, (ml)*	Intake, (ml)	Output, (ml)	Weight change, (kg)	Intake, (ml)	Output (ml)	Weight change, (kg)
C. E. R.	200 290 560	1200	900	-0.2	1160	530	+0.3
R. S. H.	220 295 385	800	510	-0.1	1500	190	+0.9
W. F. M.	270 500 770	800	390	-0.2	1300	360	+0.6
B. E. H.	195 412 770	1000	760	0.0	1500	620	+0.3

*One week control on each subject during normal activity, giving average urine volumes with minimum and maximum values for these periods above and below the average value.

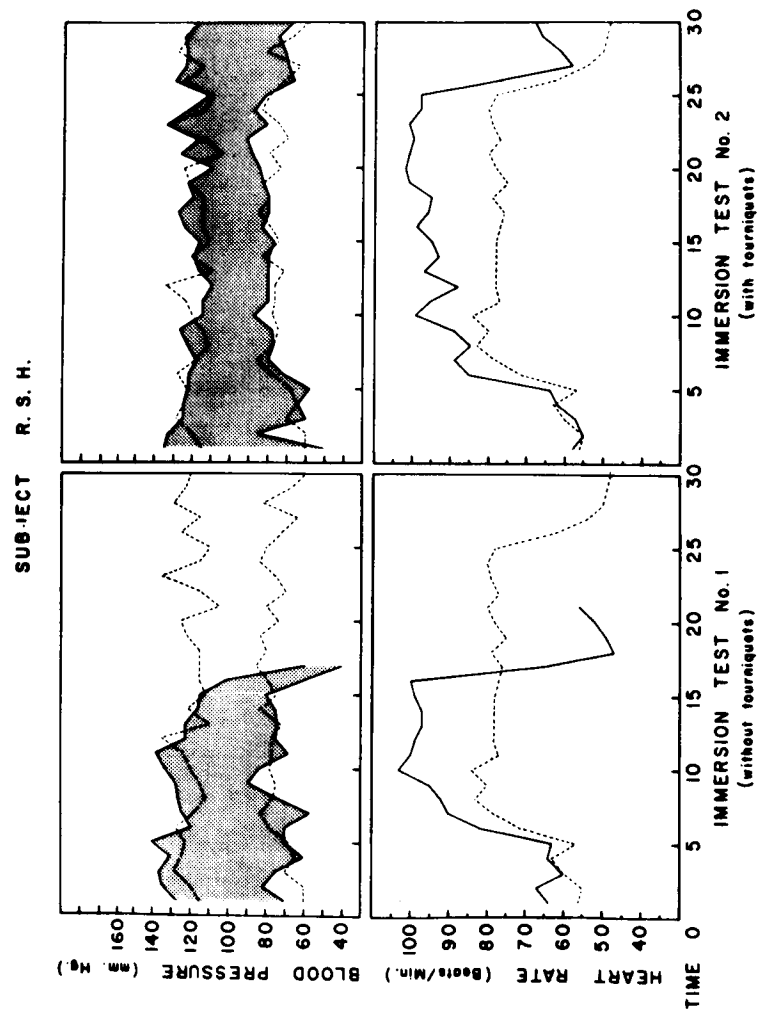
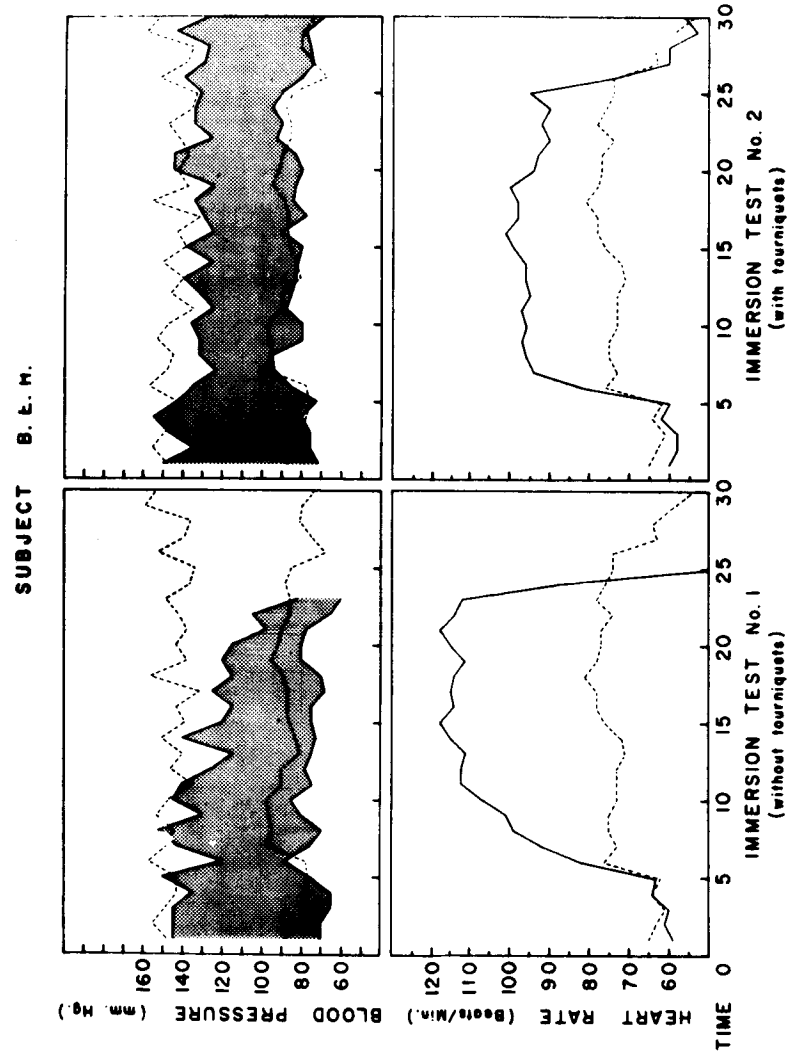


Figure 2. Blood pressure and heart rate response to tilting before and after water immersion. Tilt-up starts at time 5 minutes and tilt-down at 25 minutes unless syncope occurs and the subject is tilted down sooner. The dotted lines show results of a pre-immersion control tilt and the solid lines show the results to tilting after immersion.



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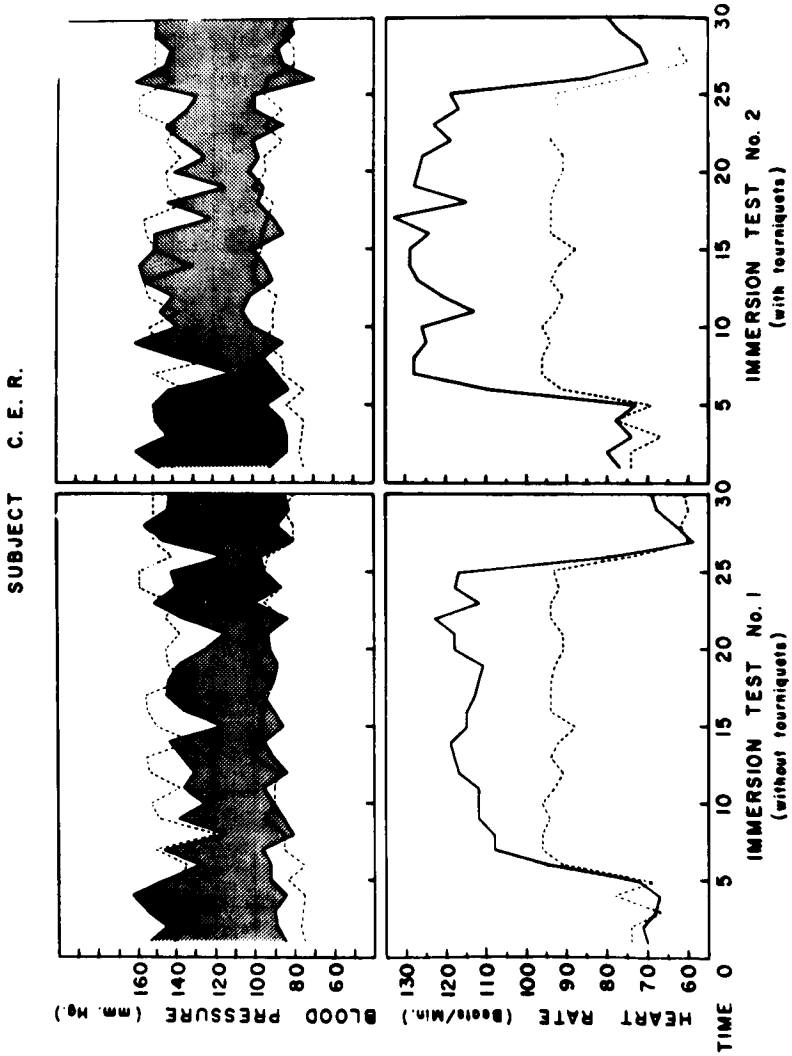

Figure 4. Blood pressure and heart rate response to tilting before and after water immersion. Tilt-up starts at time 5 minutes and tilt-down at 25 minutes unless syncope occurs and the subject is tilted down sooner. The dotted lines show results of a pre-immersion control tilt and the solid lines show the results to tilting after immersion.

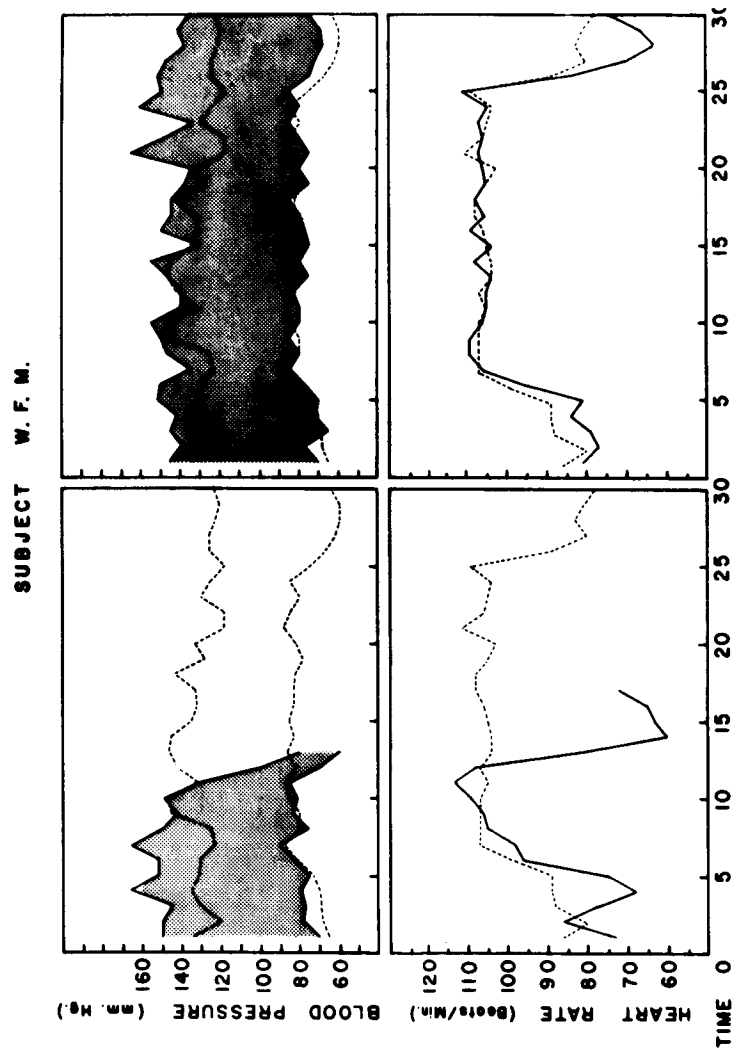

Figure 5. Blood pressure and heart rate response to tilting before and after water immersion. Tilt-up starts at time 5 minutes and tilt-down at 25 minutes unless syncope occurs and the subject is tilted down sooner. The dotted lines show results of a pre-immersion control tilt and the solid lines show the results to tilting after immersion.

BEDREST STUDIES AND TILT TABLE TOLERANCE

By Carlos Vallbona, M.D.
Texas Institute for Rehabilitation and Research

In the spring of 1963, the Texas Institute for Rehabilitation and Research began a series of studies of the effect of bedrest in healthy subjects. We became interested in carrying out these studies because we had approximately 10 years of experience on the cardiovascular and metabolic effects of paralysis. We had started studying paralysis produced by poliomyelitis and later we studied paralysis produced by spinal cord injury where a new element was added to the paralysis, namely, the sensory deprivation produced by the cutoff of the afferent impulses to the brain. We had observed orthostatic hypotension in patients with paralysis and had evaluated the effectiveness of pressure suits in these individuals. We felt that additional studies on the mechanisms of orthostatic hypotension in healthy subjects would provide us with a good opportunity to develop techniques to quantitate cardiovascular deconditioning produced by recumbency.

These studies carried out in 1963, had several objectives. The main objectives were to: (1) attempt quantitation of the cardiovascular deconditioning produced by bedrest; (2) evaluate the effectiveness of a program of isometric exercises in offsetting the cardiovascular deconditioning that may be produced by bedrest; (3) evaluate the usefulness of simultaneous recordings of the electrocardiogram and phonocardiogram in assessing the integrity of cardiac dynamics; and (4) assessing the changes in the intake and output of these individuals and the changes in calcium/phosphorus metabolism. As indicated in the previous presentation, Dr. Mack had developed a technique for studying bone densitometry. Our studies gave Dr. Mack an opportunity to evaluate the usefulness of her technique in assessing skeletal decalcification produced by bedrest.

A preliminary study was carried out in March 1963. That pilot experiment had a specific objective, which was to evaluate the cardiovascular deconditioning produced by 3 days of bedrest and to evaluate the potential protective effect of repeated controlled Valsalva maneuvers (Flack tests) during bedrest. It was observed that 3 days of bedrest caused orthostatic hypotension in some of the six subjects who were studied. Five of these subjects participated in a second period of 3 days of bedrest and performed a Valsalva maneuver for 15 seconds every 30 minutes while they were awake. It was observed that 3 of these

5 subjects developed syncope immediately after they performed a Flack test in the upright posture. The main studies of 1963 were carried out from May through September.

Figure 1 shows the calendar of these studies. The study of 3 days of bedrest was called Study I (not to be confused with the pilot study just mentioned). Six subjects were admitted to the Immobilization Study Unit that was set up at the Texas Institute for Rehabilitation and Research. They were on a period of observation for several days, a tilt test was carried out the first day of recumbency, and they stayed in bedrest for 3 days. The subjects could move in the horizontal position and were allowed one pillow, but all excretory functions were performed in the horizontal position. They were observed carefully and we believed that the conditions of bedrest were properly carried out according to the conditions stipulated in the protocol. The subjects were kept on observation following bedrest and then dismissed on a leave of absence. The same six subjects participated in the second period of bedrest for 3 days. The conditions of the bedrest were identical to the first period with one exception. Isometric exercises were carried out 4 times a day according to a program that will be discussed by Dr. Beasley.

Study II was carried out in July, August, and September of 1963. This study aimed at evaluating the effects of 14 days of bedrest. Six individuals were admitted to the hospital and kept on observation. They were able to walk about and could go out of the hospital, but intake and output were carefully measured. They remained in the horizontal position for 14 days. Tilt studies were carried out on the first day of bedrest and repeated after bedrest. Ergometry studies were carried out before and after bedrest. The subjects were kept on observation after the period of bedrest. One of the subjects had to go back to school and could not participate in the second period so a new subject was added. They participated in a 14-day period of bedrest with isometric exercises added to the conditions described for the first period.

In order to carry out all of the studies that were contemplated, an experimental design had to be prepared. Many studies had to be conducted and the planning and setting up of procedures for the studies were difficult tasks. We approached it from the standpoint of a program evaluation review technique. From the setting up of the experimental design until the individuals were discharged from the hospital on a leave of absence, a complete set of tasks had to be planned and these are shown on figure 2.

One major part of these studies consisted of the tilt experiments that were carried out immediately before and after bedrest. Figure 3 shows the tilt table that was used. It was the same motorized tilt table used for several years in our tilt studies of patients with paralysis. A special saddle was built in order to do the tilt studies with the feet unsupported. The use of suspension straps to support the body in the

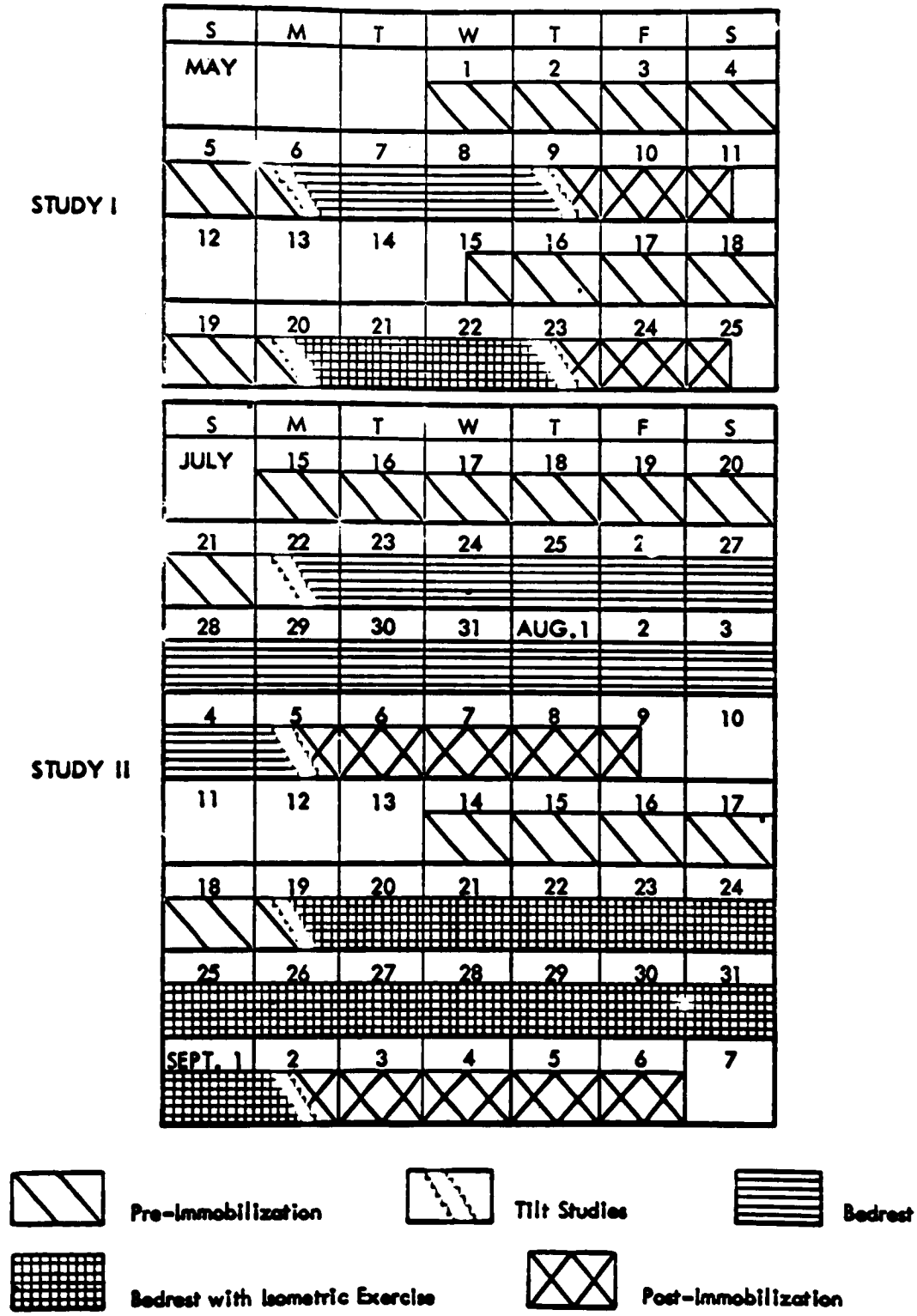

Figure 1.- Calendar for studies.

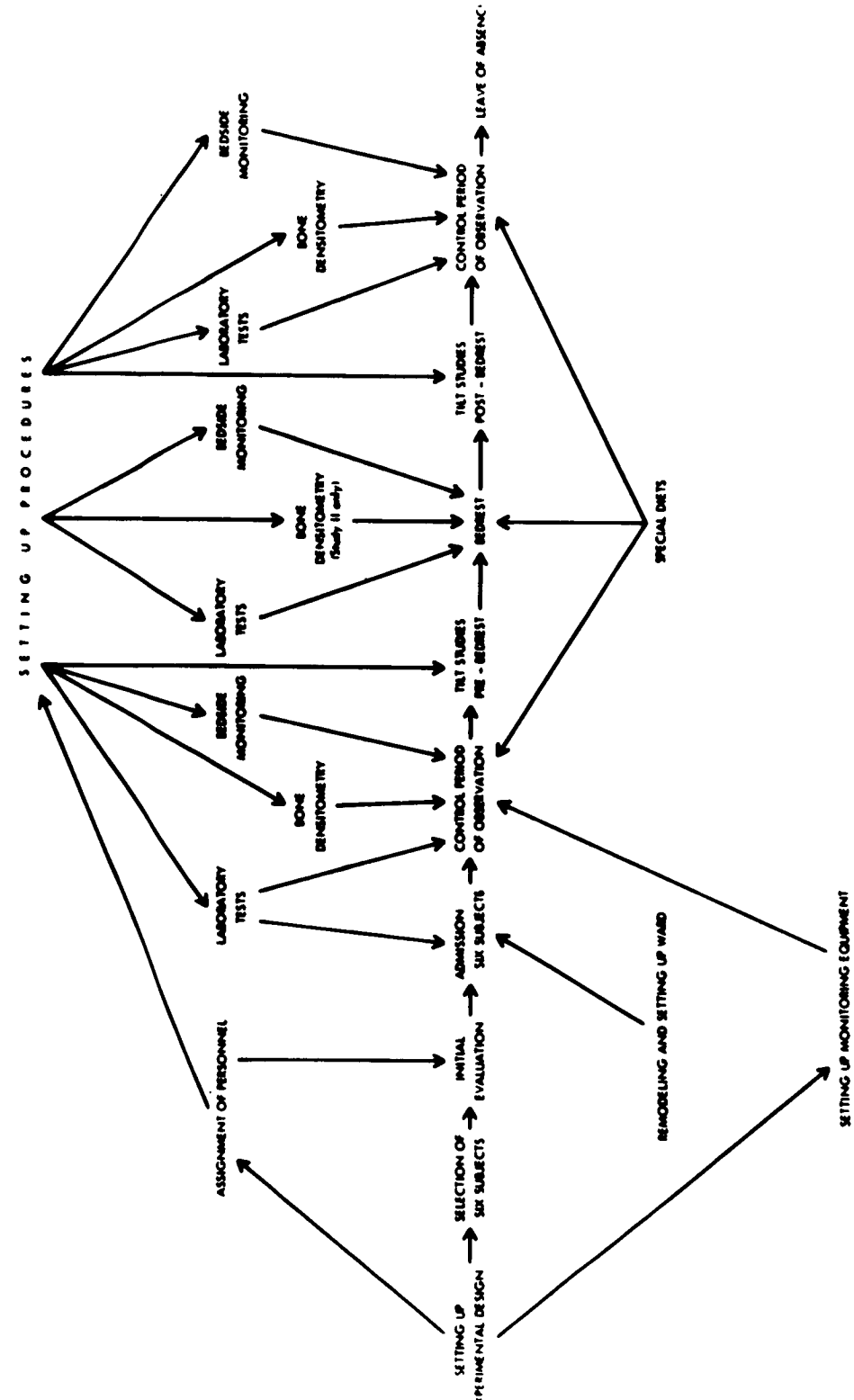

Figure 2.- Tasks for the studies.

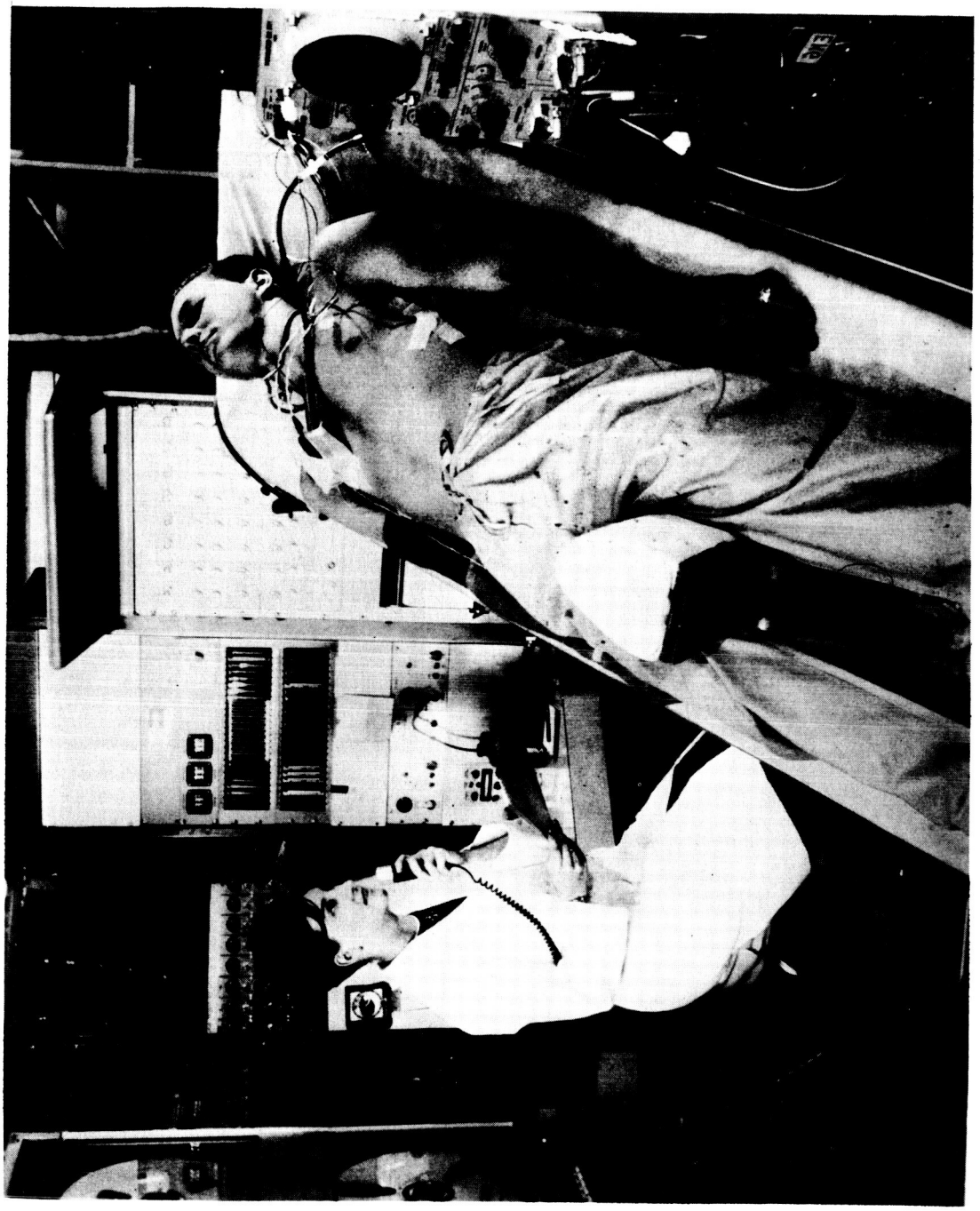

Figure 3.- Tilt table used for studies.

tilt position may produce excessive pressure in the inguinal region, cut off blood supply to the lower extremities, and prevent venous return. This caused severe intolerance in one subject.

The variables recorded included: (a) the electrocardiogram obtained from a transthoracic lead; (b) the same two electrodes to record impedance changes across the chest; (c) the phonocardiogram; (d) the carotid pulse tracing detected with a pulse pickup placed on the neck; (e) the radial pulse tracings obtained from another crystal microphone placed on the wrist; (f) the blood pressure recorded by electrosphygmography; (g) and also, in all the tilt studies, an intraarterial (brachial) blood pressure record. The variables were displayed on-line in analog form on an oscilloscope and by a direct writing instrument. They are recorded also on magnetic tape for future playback and analysis.

The tilts varied in duration in the first study and in the second study. The results presented pertain to the second study where the tilts lasted for 15 minutes (fig. 4). The details of the procedure and the analysis of results are described in the contractor's report.[1]

The objective of the analysis of analog records was to evaluate the effect of bedrest on the cardiovascular tolerance to tilt. Figure 5 shows the differences in analog records between two subjects; one who tolerated tilt after bedrest and one who did not. Figure 5 is being shown for one purpose; this figure is composed of several yards of records on these two individuals and at first glance it might seem to be an easy task to analyze the differences that occur in each subject. One must keep in mind, however, that to compose this figure, we had to go through many, many search and analytic procedures.

Figure 5 shows the type of analog record gotten on each subject. Yards and yards (perhaps miles) of this type of record were obtained and we had to decide on the techniques to quantitate the changes effected by bedrest.

Equipment was available for a completely automatic processing of data. We had the physiological events, electrical transduction, analog display of data, and storage of records in analog tape. Techniques were available for automatic analog to digital conversion, computation, and display and interpretation of the results (fig. 6), but application of these techniques to the processing and analysis of our data was plagued with difficulties. Simple conversion of data from analog to digital form would have created the problem of what to do with a large pile of numbers before meaningful information could have been obtained.

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[1]NAS 9-1461 CR-172

The situations which were analyzed for the second study were the following: steady state at 0° (situation 01); immediately after reaching 70° (situation 02); steady state before the end of tilt (situation 03); immediately after return to 0° (situation 04); steady state at 0° (situation 05); during Valsalva maneuver (situation 06); and final steady state at 0° (situation 07).

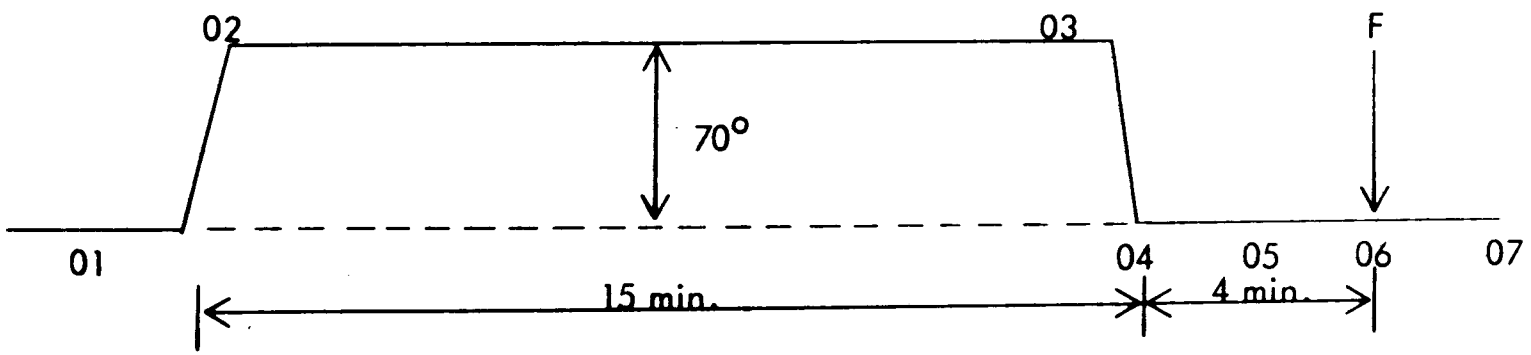


Figure 4.- Tilts for second study.

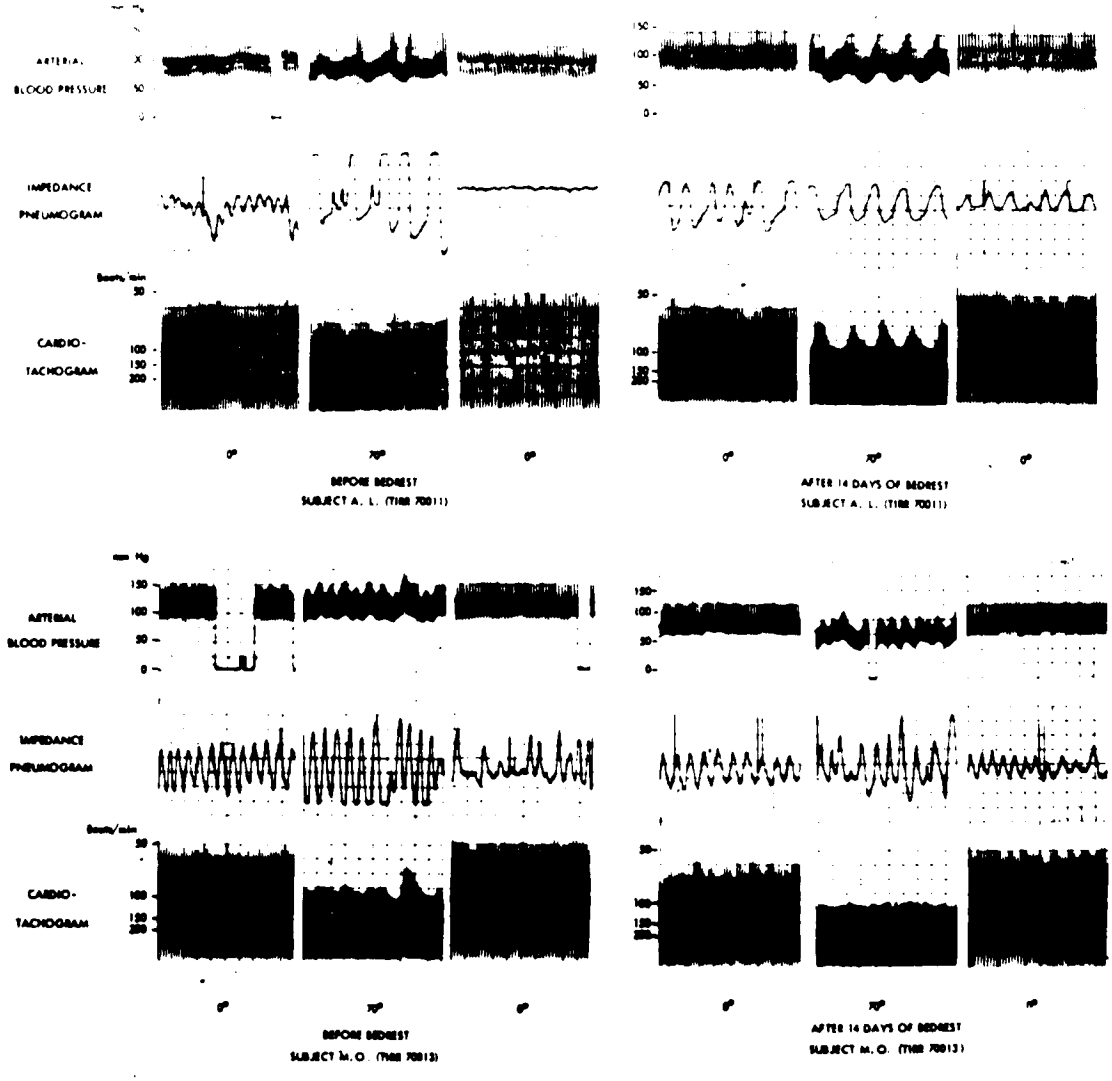


Figure 5.- Difference in analog records between two subjects.

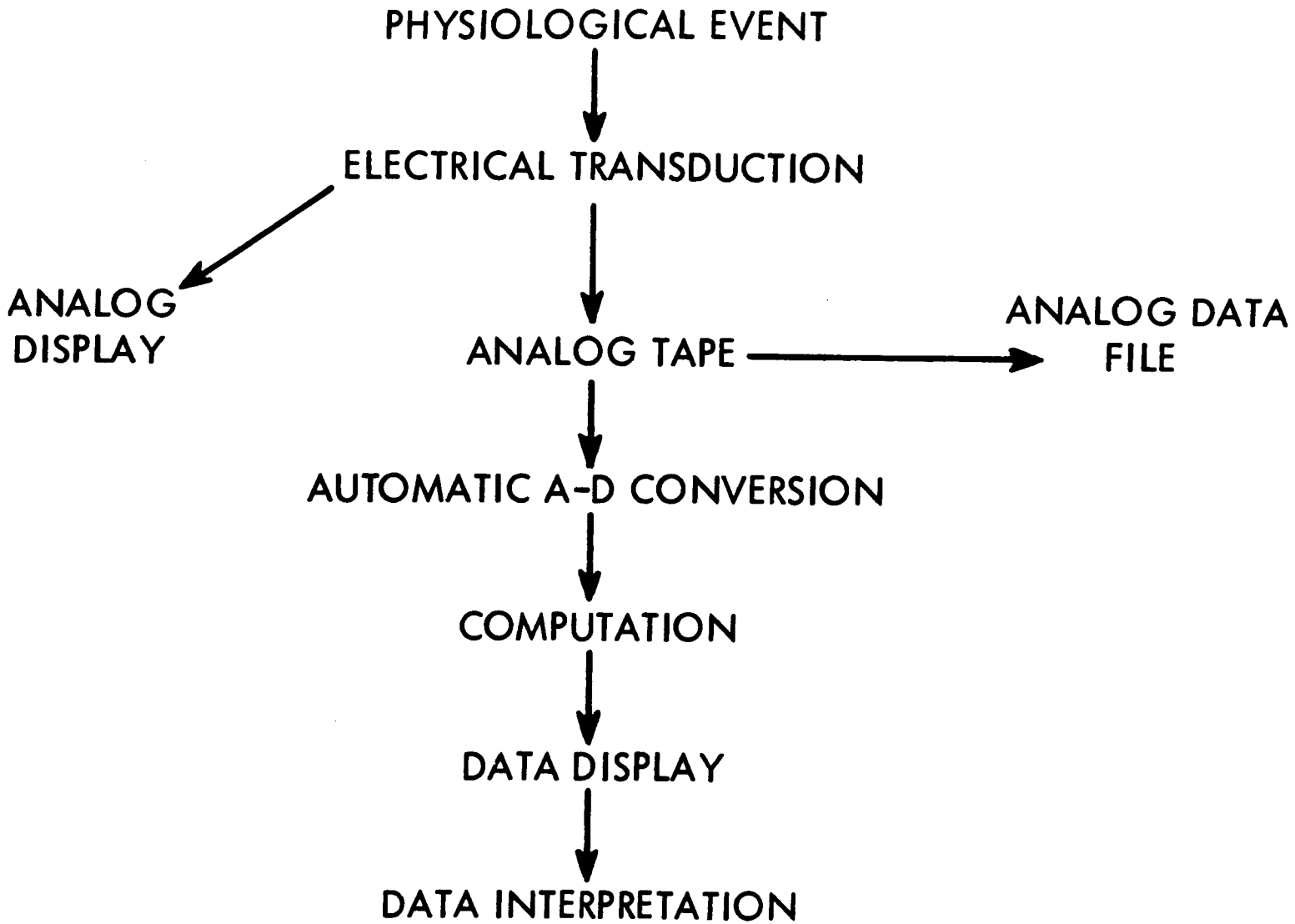


Figure 6.- Techniques for automatic analog to digital conversion, computation, and display and interpretation of the results.

Since we had to report the results to the Manned Spacecraft Center shortly after the studies, it was necessary to take a seemingly more complicated route (fig. 7). It consisted of recording the physiological events with careful coding of analog data so that searching for rapid playback could be achieved, either automatically or semi-automatically. (The unit we had for automatic coding and searching left much to be desired. However, for the studies carried out this year, the problem has been solved.) We then edited the playback records for point recognition and noise discard. In essence, we were preprocessing the data ahead of the computer. We did a semi-automatic analog to digital conversion. Data were obtained on punch cards and programs were written for computer transformation of the data, digital plot display, tabulation of individual data, editing and correction, recognition and interpretation, statistical analysis, and establishment of conclusions.

We kept two types of records on our playback, which were fast speed and slow speed records. The fast speed records were of the electrocardiogram, phonocardiogram, carotid pulse tracing and radial pressure pulse tracing. Through the program of semi-automatic tape analog to digital conversion, we were able to establish a digital figure at each one of the points shown on figure 8. By simple application of a basic formula, we could measure the RR interval beat by beat for a certain length of the record, the duration of the mechanical systole plus excitation period, the duration of diastole, the duration of the isotonic phase, the duration of the isometric phase, the time interval from Q to the first heart sound, and the time interval between the first and the second heart sounds. By application of the formula shown on figure 8, we were able to measure the pulse wave velocity. A computer program was written that allows for editing of the digital data and automatic discarding of data that do not fulfill certain criteria given to the computer.

The results are expressed in computer output form (fig. 9). Observation 1 means beat 1, observation 2 means beat 2, et cetera, throughout a period of 15 seconds. A, B, C, D, E, and F are the digital readouts at each one of the points shown on the previous figure. The variables derived from these digital data are: T - the time from onset of Q of the electrocardiogram to the first heart sound; S - time of systole; D - time of diastole; I - time of isotonic phase; X - time interval between the first and second heart sounds; M - time of isometric phase; V - the pulse wave velocity; and R - duration of the cardiac cycle. S', I', and M' are the predicted values of systole, isotonic phase, and isometric phase for each particular beat.

It is well known that the duration of the cardiac cycle and its phases are dependent on the heart rate. The relationship between these variables has been expressed mathematically. We incorporated these

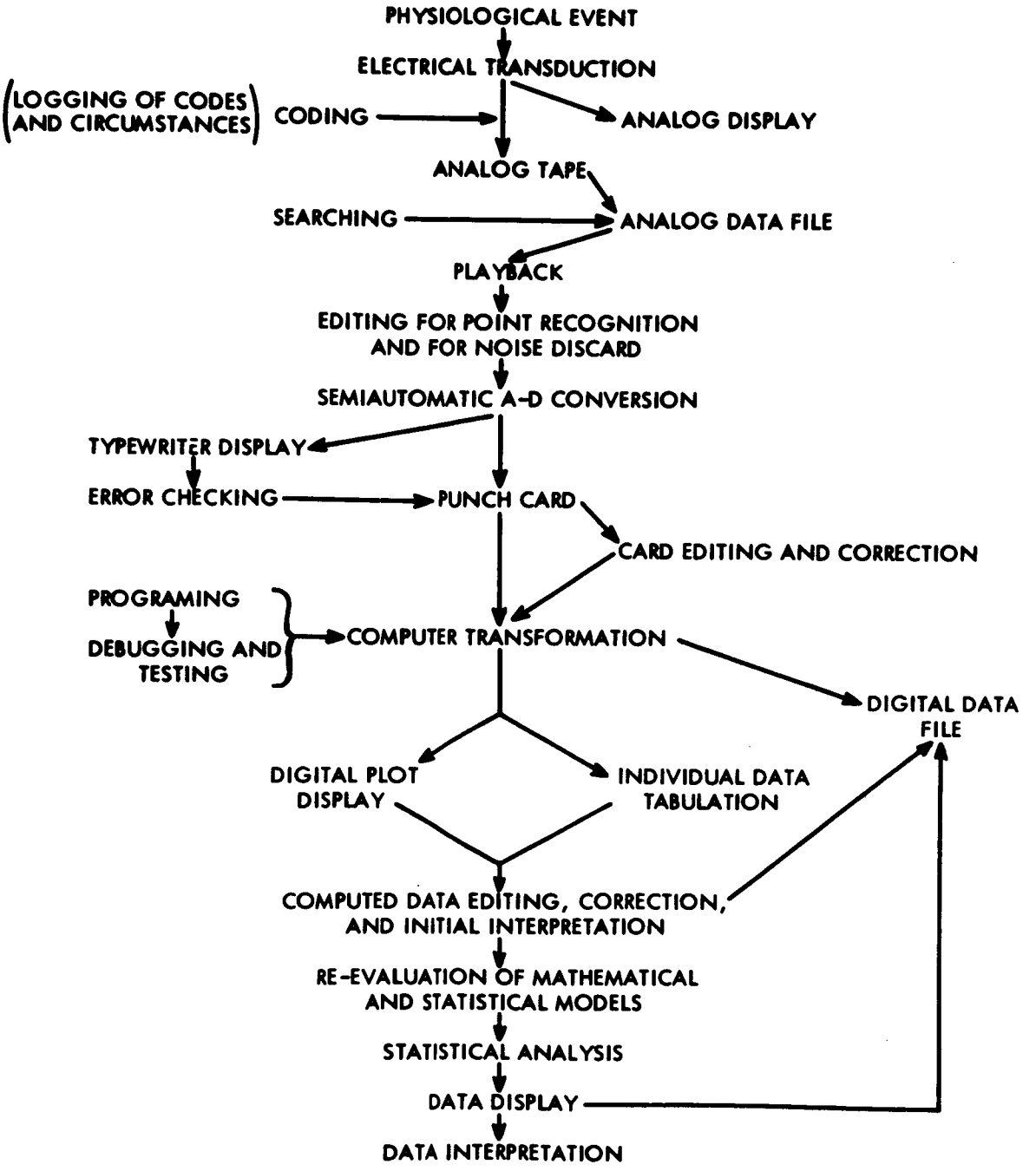
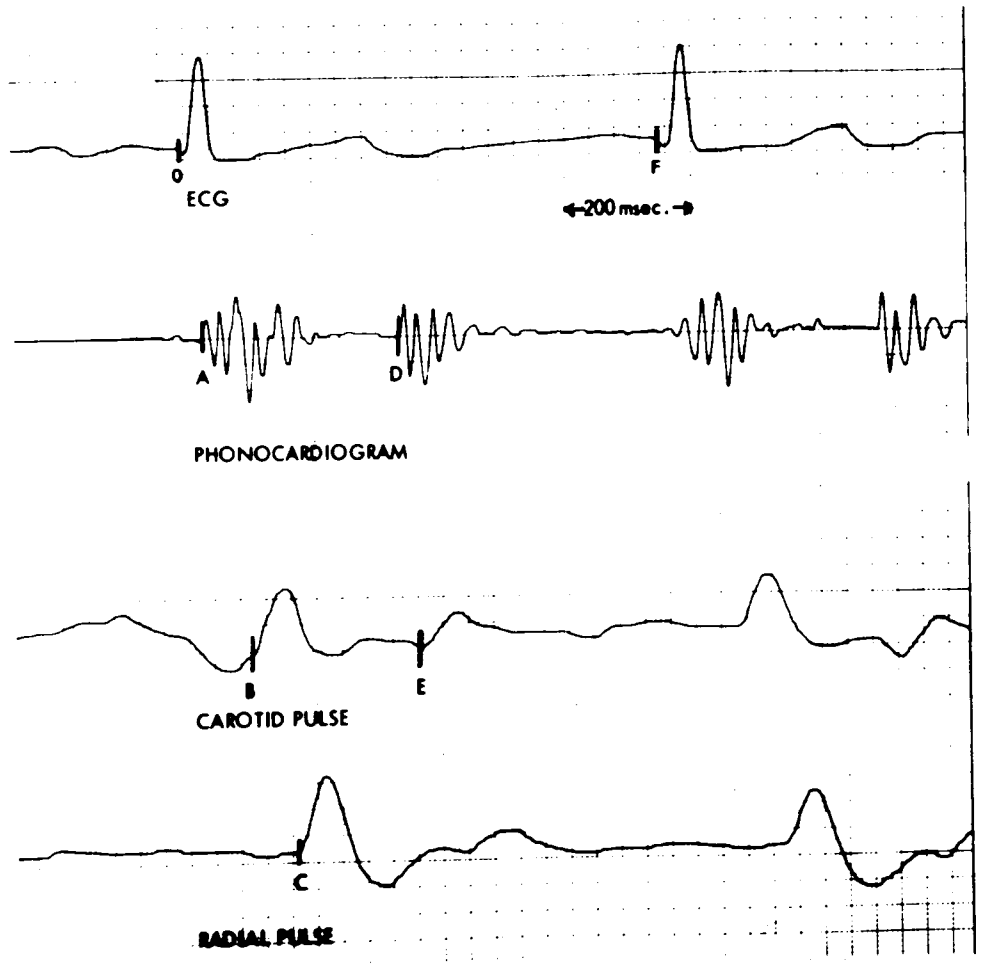


Figure 7.- Recording of physiological events with coding of analog data.



F = RR Interval (R)

D = Mechanical Systole plus Excitation Period (S)

F - D = Diastole (D)

E - B = Isotonic Phase (I)

D - (E - B) = Isometric Phase (M)

D - A = 1st to 2nd Sound (X)

A = Q to 1st Sound (T)

$$\frac{\text{Stern. to Rad. - Stern. to Car.}}{\text{B - A}} = \text{Pulse Wave Velocity (V)}$$

Figure 8.- Digital figure points for fast speed records of electrocardiogram, phonocardiogram, carotid pulse tracing, and radial pressure pulse tracing.

```
                    •••••••••THE DATE OF THIS REPORT FOR TILTS IS 7/6/64••••••••••
82.  697.  420.  L    N E. A. C.    70011/POSIT    1/TIME   9070/DATE  90263     CALIB.  37621 .265821

  OBSERVATION    1
    A            B          C          D          E          F
   164.         278.       717.       1425.      1524.      3841.

    T            S          I          X          M           V          R          S'         I'         M'
   43.59        374.79     331.21     335.19     47.58       5.27      1021.[illegible] 394.07  305.60     88.47

  OBSERVATION    2
    A            B          C          D          E          F
   2[illegible]0.  370.    706.       1449.      1558.      3848.

    T            S          I          X          M           V          R          S'         I'         M'
   53.16        385.17     315.79     332.00     69.38       6.89      1022.86    394.43     305.80     88.64

  OBSERVATION    3
    A            B          C          D          E          F
   227.         4[illegible]8.  736.  1475.      1565.      3959.

    T            S          I          X          M           V          R          S'         I'         M'
   60.34        392.04     307.55     331.74     84.53       7.05      1052.37    400.08     308.81     91.27

  OBSERVATION    4
    A            B          C          D          E          F
   197.         381.       709.       1424.      1532.      4095.

    T            S          I          X          M           V          R          S'         I'         M'
   52.37        374.52     305.95     326.16     72.57       7.05      1088.52    406.89     312.43     94.47

  OBSERVATION    5
    A            B          C          D          E          F
   195.         384.       695.       1401.      1553.      4216.

    T            S          I          X          M           V          R          S'         I'         M'
   52.63        372.41     305.42     319.78     65.99       7.44      1120.64    412.86     315.58     97.26
```

Figure 9.- Results expressed in computer output form.

equations in the computer program and it was easy to establish the predicted values for systole time and for isotonic and isometric phases of the contraction.

Figure 10 shows the computer output of the averages and standard deviations of each one of these values over a period of 15 seconds. The computer program also permitted the contrasting of the actual values of each of these variables with what the computer indicated would be acceptable for the heart rates of each record. The computer did not consider invalid any values since they fell within the acceptable range.

The slow speed records permitted us to digitize, at regular intervals, the heart rate (from the cardiotachogram), the respiratory rate, and the arterial blood pressure (from the intraarterial records and from the electrosphygmomanometer). A computer program was written to tabulate these values at regular intervals, usually, twice every 30 seconds. The computer report displayed the cuff measurements for systolic and diastolic blood pressure, intraarterial measurements for systolic or diastolic blood pressure, heart rate, pulse pressure, and mean pressure (fig. 11).

The digital values did not mean much to us. Since physicians are graphically minded, we programmed the computer to prepare a display of the data in graphic form. Figure 12 shows plots obtained with an IBM 7094 computer. The graph shows the changes in heart rate, in systolic blood pressure, in diastolic blood pressure, in the mean blood pressure, and in the pulse pressure on an individual who, from a clinical standpoint, tolerated the tilt after bedrest without difficulties. Figure 12 also shows the changes in heart rate and blood pressure on an individual who developed orthostatic hypotension and impending syncope and had to be tilted back to the horizontal position in the tilt test after bedrest.

After looking at the individual plots, we believe that a good statistical model describing changes produced by bedrest in each group of individuals would be a simple averaging of the values at regular intervals from the onset of the tilt (indicated by T_1) and following the tilt down to the horizontal position (D_1). However, the statistical results did not agree with our clinical observations. Figure 13 presents the average results for 6 subjects before and after bedrest. By looking at these graphs, one may believe that the tilts after bedrest were better tolerated than those before bedrest. This did not agree with our clinical observations since three individuals developed orthostatic hypotension and impending syncope after bedrest. There was a difference reflected in the negative slope of the pulse pressure. Therefore, we concluded another statistical model would be more useful in quantifying cardiovascular deconditioning in individuals.

••••••••THE DATE OF THIS REPORT FOR TILTS IS 7/6/64••••••••••

96. 673. 453. L : E. A. C. 70011/POSIT 3/TIME 10030/DATE 72263 CALIB. 3741(.26731)

AVERAGE T	AVERAGE S	AVERAGE I	AVERAGE X	AVERAGE M	AVERAGE V	AVERAGE R	AVERAGE S'	AVERAGE I'	AVERAGE M'
47.22	92.16	218.57	254.94	43.59	10.56	811.53	361.70	268.06	73.65
STD.DEV. T	STD.DEV. S	STD.DEV. I	STD.DEV. X	STD.DEV. M	STD.DEV. V	STD.DEV. R	STD.DEV.S'	STD.DEV.I'	STD.DEV.M'
3.76	6.41	8.18	5.55	6.81	2.66	148.14	5.06	2.78	2.28
RATIO T/M'	RATIO S/S'	RATIO I/I'	RATIO X/I'	RATIO M/M'	RATIO T/M	RATIO X/I			
0.641175	0.255377	0.758787	0.885028	1.134945	0.564943	1.166375			

	RANGE OF S		RANGE OF I		RANGE OF V		RANGE OF R	
	MIN	MAX	MIN	MAX	MIN	MAX	MIN	MAX
CALCULATED	296.84	347.48	185.79	251.36	5.54	14.78	486.92	1136.15
ACTUAL	290.94	309.66	258.75	283.58	9.52	11.75	372.40	900.96

Figure 10.- Computer output of the averages and standard diviation of each cardiac cycle and its phases and the heart rate for a period of 15 seconds.

SUBJECT NO 70067 DATE 50683 HOUR 4C01 PAGE

TIME T1-T	CBP Y1	AHPS Y2	ARPD Y3	HR Y4	DY	YM	DY2	YM2
2.64	156.	0.	0.	87.	0.	0.	74.	87.
2.51	62.	0.	0.	87.	0.	0.		
1.73	128.	130.	77.	90.	55.	95.	64.	87.
1.62	64.	130.	74.	87.	56.	93.		
0.61	140.	140.	77.	84.	63.	90.	81.	86.
0.48	59.	134.	78.	78.	56.	97.		
T1+T								
0.41	0.	133.	77.	93.	56.	93.	0.	0.
0.53	0.	118.	69.	94.	49.	85.		
1.55	136.	119.	79.	106.	40.	92.	64.	93.
1.46	72.	125.	90.	104.	35.	102.		
2.37	0.	127.	78.	103.	49.	94.	0.	0.
2.48	71.	131.	79.	104.	52.	96.		
D1+T								
0.06	0.	128.	82.	101.	46.	97.	0.	0.
0.20	0.	143.	87.	91.	56.	106.		
1.08	138.	0.	0.	85.	0.	0.	75.	88.
1.21	63.	0.	0.	87.	0.	0.		
2.07	136.	132.	81.	89.	51.	94.	76.	89.
2.20	60.	133.	76.	81.	57.	95.		
3.08	145.	146.	86.	79.	60.	106.	70.	94.
3.19	75.	144.	87.	92.	57.	106.		
4.03	0.	134.	77.	91.	57.	96.	0.	0.
4.15	67.	135.	79.	80.	56.	98.		
5.05	138.	133.	79.	75.	55.	96.	79.	89.
5.19	59.	129.	78.	82.	51.	95.		
6.00	138.	124.	92.	73.	32.	104.	71.	91.
6.12	67.	0.	0.	74.	0.	0.		
7.02	145.	137.	81.	81.	56.	100.	83.	90.
7.16	62.	126.	75.	71.	51.	92.		
7.99	132.	119.	77.	81.	42.	91.	75.	82.
8.12	57.	124.	74.	75.	50.	91.		

Figure 11.- Computer report displaying cuff measurements for systolic and diastolic blood pressure, intraarterial measurements for systolic or diastolic blood pressure, heart rate, pulse pressure, and mean pressure.

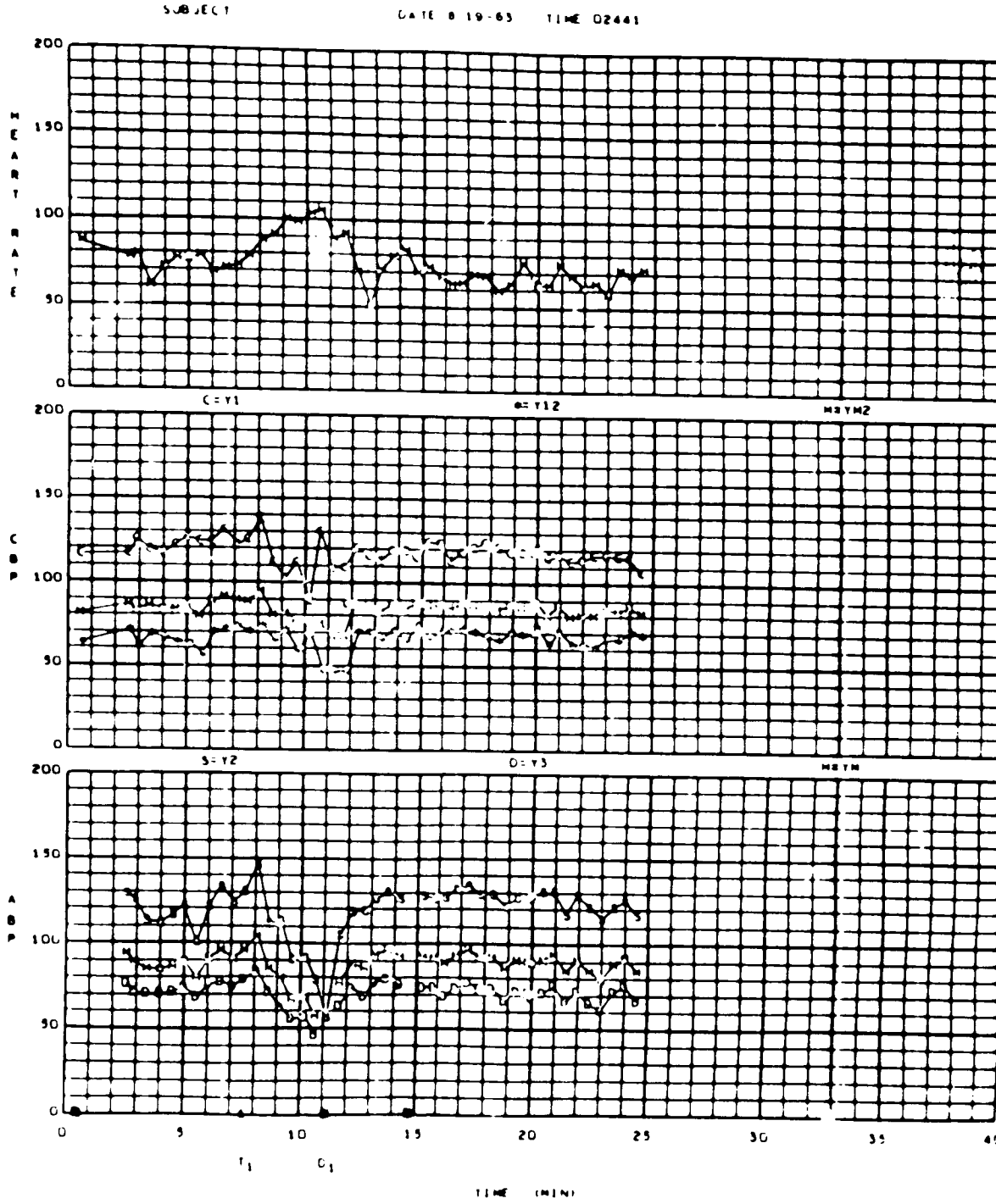


Figure 12.- Plots obtained with an IBM 7094 computer.

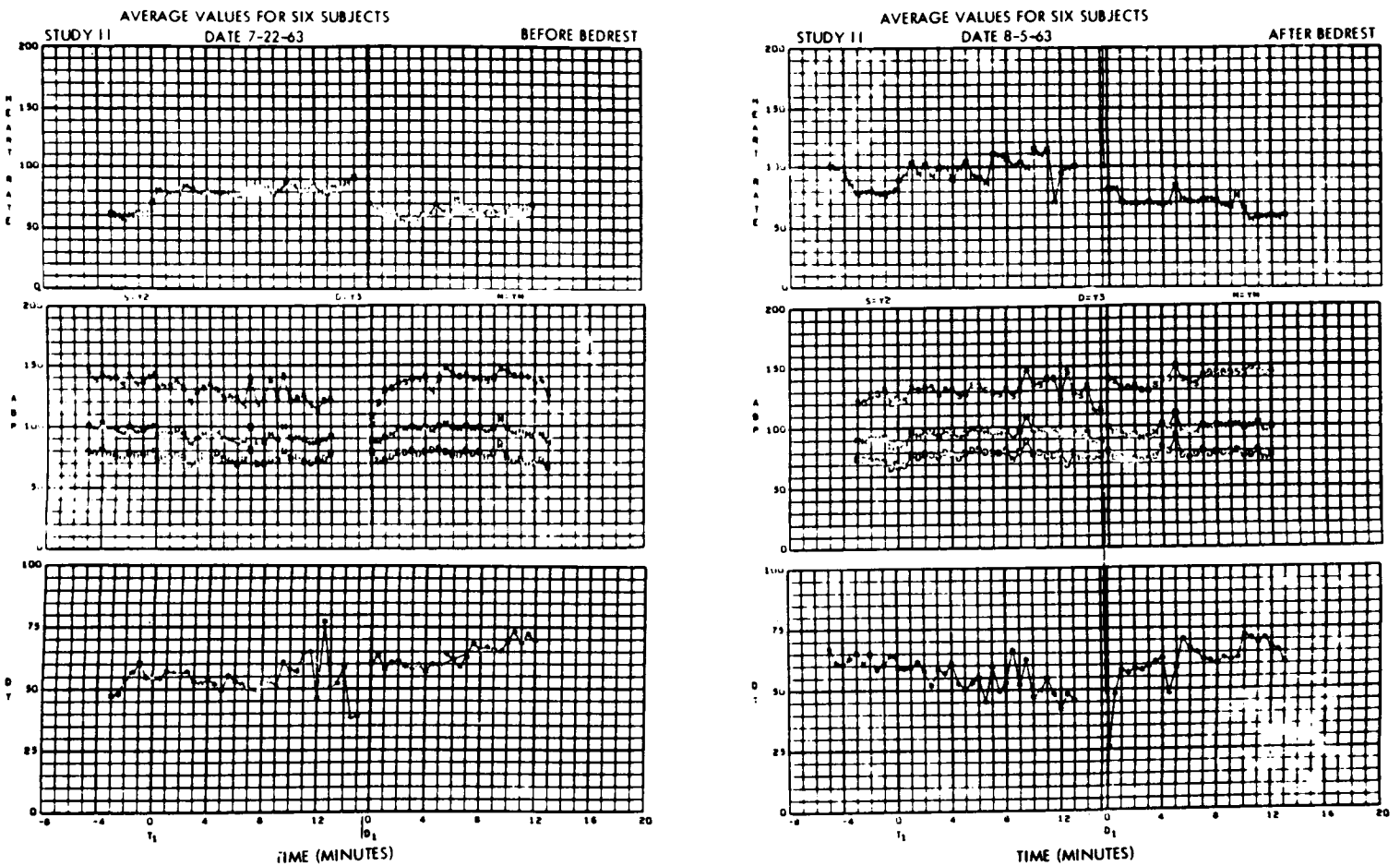


FIGURE 1

Figure 13.- Average results of 6 subjects before and after bedrest.

It was decided to measure on each individual the slope of blood pressure changes and heart rate changes throughout the tilt tests. Figure 14 shows the computer output of this data. This figure is shown to indicate that this is a matrix computer output of difficult interpretation unless each field is labeled. Since this output report did not clearly show the individual data, we requested a computer output of these data on a more didactic form (fig. 15). Thus, it was possible to establish the average slope for the group. At 0°, of course, there was no significant slope for the systolic blood pressure, the diastolic blood pressure, or the mean blood pressure. During the tilt procedure before bedrest, the slope was not significant either but after bedrest there was a negative slope of the mean pressure (fig. 16). We had now completed an analysis of variance of these slopes and significance of results which are shown in these figures had been confirmed by this analysis of variance.

The analysis of slopes of blood pressure in the tilts following bedrest with isometric exercises showed that the slopes were slightly negative, but not significantly different than the slopes of the tilts before bedrest. This suggests that the iosmetric exercises had a protective effect on these individuals.(fig. 17).

These are, in essence, the results of the studies conducted in 1963. During the last year, we have been able to carry out similar studies in individuals with quadriplegia. The same methodology has been followed and it was not surprising that the subjects with quadriplegia had a very clearcut intolerance to the tilt procedures. The slope of the blood pressure changes was more negative and steep than the ones observed in healthy subjects following bedrest. In collaboration with Dr. Lipscomb, we have undertaken a study of the adrenal responses of these individuals to passive tilt. We have observed clearcut differences in the behavior of the patient with paralysis and the behavior of the healthy individual after bedrest; the differences probably being due to the denervation produced by the spinal cord injury in the quadriplegic patient. Although denervation did not occur in our individuals following bedrest, one has to keep in mind that sensory deprivation may effect the regulatory centers of cardiovascular regulation.

	SUBJECT # (100 16)	DATE (8 5 63)						
Average Syst. B.P.	2.0461	130.5454	.8437	σ 5.7509	11.0000	1 1 16 5	1	RESULTS AT 0° BEFORE TILT
	22.5300	1436.0000	53.2649	187794.0000	2923.3600	1 1 16 5		
Diast. B.P.	2.0481	72.7272	.8437	5.4422	11.0000	1 2 16 5	1	
	22.5300	800.0000	53.2649	58478.0000	1614.4900	1 2 16 5		
Heart Rate	1.7507	74.1428	.9669	4.1111	14.0000	1 3 16 5	1	
	24.5100	1038.0000	55.0651	77180.0000	1781.0200	1 3 16 5		
Different. B.P.	2.0481	57.8181	.8437	3.2808	11.0000	1 4 16 5	1	
	22.5300	636.0000	53.2649	36880.0000	1308.8700	1 4 16 5		
Mean B.P.	2.0481	91.9090	.8437	5.1469	11.0000	1 5 16 5	1	
	22.5300	1011.0000	53.2649	93185.0000	2050.0700	1 5 16 5		
Slopes Syst. B.P.	1.4250	131.2243	.8453	18.6377	12.0000	2 1 16 5		RESULTS DURING TILT POSITION
	-19.7441	a 158.6471	σ_{xy} 9.5377	σ_a 3.4026	-.8728	2 1 16 5	2	
	2910.9472	910.0626	2910.9472	91.0062	F 31.9862	2 1 15 5		
Diast B.P.	1.1145	84.6713	.7905	9.1243	11.0000	2 2 16 5		
	-8.5630	95.9218	6.4486	2.5794	-.7419	2 2 16 5	2	
	458.2809	374.2630	458.2809	41.5847	11.0203	2 2 16 5		
Heart Rate	1.4250	86.8333	.8453	13.4761	12.0000	2 3 16 5		
	-8.4347	98.8529	11.9934	4.2778	-.5290	2 3 16 5	2	
	559.2267	1438.4403	559.2267	143.8440	3.8877	2 3 16 5		
Diff. B.P.	1.3145	50.3636	.7905	6.2333	11.0000	2 4 16 5		
	-6.7502	59.2371	3.3955	1.3582	-.8561	2 4 16 5	2	
	284.7805	103.7654	284.7805	11.5294	24.7001	2 4 16 5		
Mean B.P.	1.3145	101.4895	.7905	10.5434	11.0000	2 5 16 5		
	-10.8960	115.8128	6.4086	2.5634	-.8169	2 5 16 5	2	
	742.0108	369.6392	742.0108	41.0710	18.0665	2 5 16 5		
Average Syst. B.P.	1.6160	112.5333	1.0190	σ 22.9529	15.0000	1 1 16 5	1	RESULTS AT 0° AFTER TILT
	24.2400	1688.0000	53.7090	197332.0000	3023.6800	1 1 16 5		
Diast. B.P.	1.8430	64.3076	.8901	8.2298	13.0000	1 2 16 5	1	
	23.9600	836.0000	53.6680	54574.0000	1619.0700	1 2 16 5		
Heart Rate	1.6160	55.4666	1.0190	5.7801	15.0000	1 3 16 5	1	
	24.2400	832.0000	53.7090	46616.0000	1373.2700	1 3 16 5		
Differential B.P.	1.8430	55.3076	.8901	6.7624	13.0000	1 4 16 5	1	
	23.9600	719.0000	53.6680	40315.0000	1386.2000	1 4 16 5		
Mean B.P.	1.8430	82.7692	.8901	10.0842	13.0000	1 5 16 5	1	
	23.9600	1076.0000	53.6680	90280.0000	2080.2500	1 5 16 5		

Figure 14.- Measurements of each individual for the slope of blood pressure changes and heart rate changes throughout the tilt tests.

SUBJECT # 70008 DATE 5/ 6/63

RESULTS IN SUPINE POSITION BEFORE TILT

	MEAN	ST DEV	N
BP SYST	123.7	4.4	7
BP DIAST	66.7	3.0	7
H. R.	69.3	3.9	8
PULSE PRESS	57.0	2.2	7
MEAN PRESS	85.5	3.4	7

RESULTS DURING TILT

	MEAN	ST DEV	INTERCEPT	ST DEV	SLOPE	ST DEV	N	F
BP SYST	125.7	21.4	163.9	5.8	-21.38	3.4	4	37.9
BP DIAST	76.2	14.2	100.6	6.1	-13.63	3.6	4	14.1
H. R.	86.1	3.3	83.9	3.4	1.40	1.7	6	.6
PULSE PRESS	49.5	7.9	63.3	2.9	-7.75	1.7	4	20.0
MEAN PRESS	93.0	16.4	121.7	5.9	-16.07	3.5	4	20.6

RESULTS IN SUPINE POSITION AFTER TILT

	MEAN	ST DEV	N
BP SYST	121.7	4.2	4
BP DIAST	74.4	29.4	5
H. R.	58.7	2.4	7
PULSE PRESS	60.5	4.7	4
MEAN PRESS	81.2	1.5	4

RESULTS DURING TILT WITH PROVOCATIVE VALSALVA MANEUVER

	MEAN	ST DEV	INTERCEPT	ST DEV	SLOPE	ST DEV	N	F
BP SYST	137.3	18.6	203.1	12.9	-10.28	3.3	9	9.5
BP DIAST	84.7	11.4	123.3	8.4	-6.02	2.1	9	7.8
H. R.	97.1	5.8	86.9	5.7	1.58	1.4	9	1.1
PULSE PRESS	52.5	8.6	79.7	6.8	-4.25	1.7	9	5.8
MEAN PRESS	102.2	13.6	150.3	9.4	-7.52	2.4	9	9.5

RESULTS IN SUPINE POSITION AFTER TILT

	MEAN	ST DEV	N
BP SYST	122.5	7.0	4
BP DIAST	66.2	6.8	4
H. R.	61.8	4.3	7
PULSE PRESS	56.2	7.6	4
MEAN PRESS	84.7	5.8	4

Figure 15.- Computer output of data on a more didactic form.

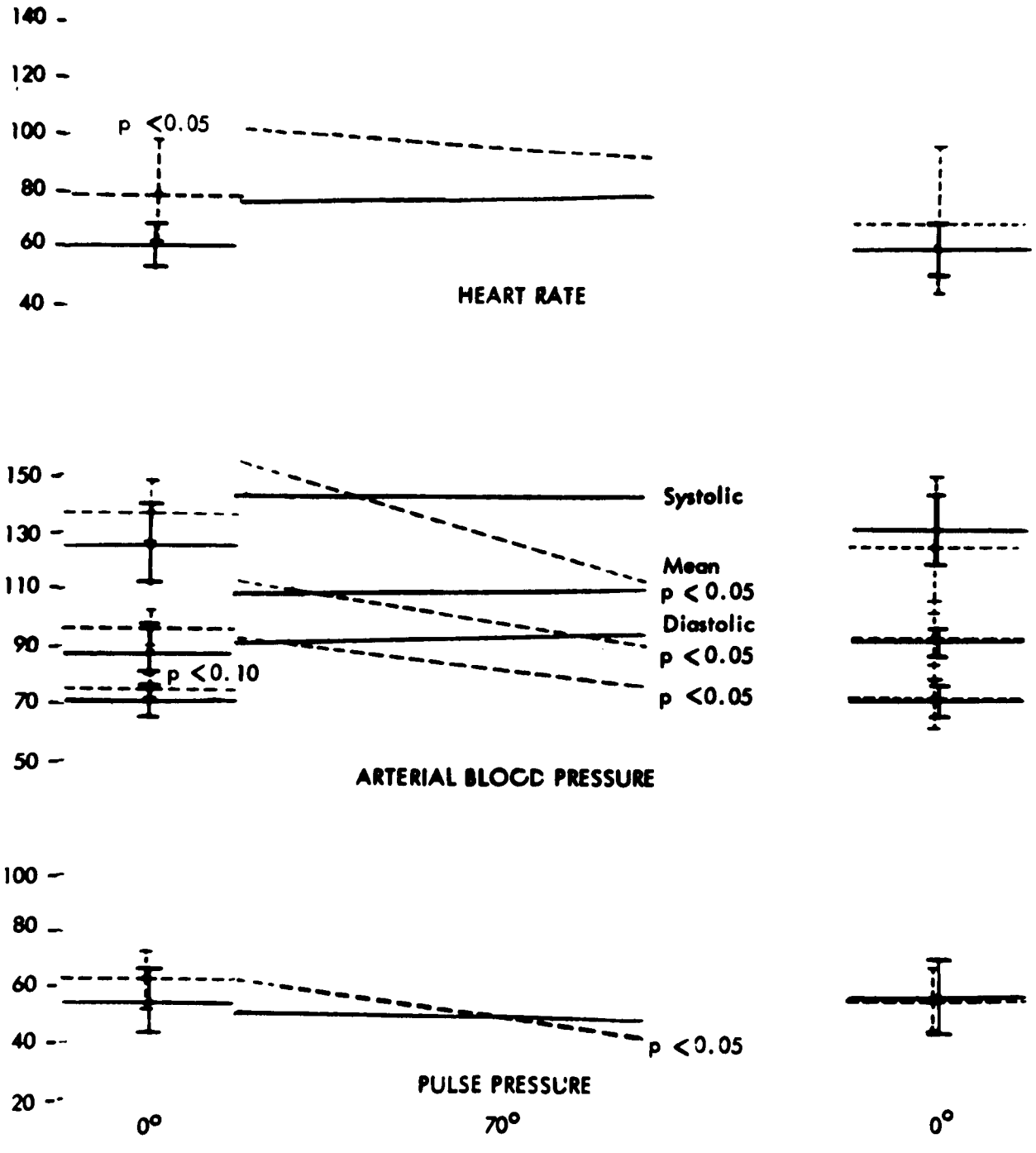


Figure 16.- Negative slope of the mean pressure after bedrest.

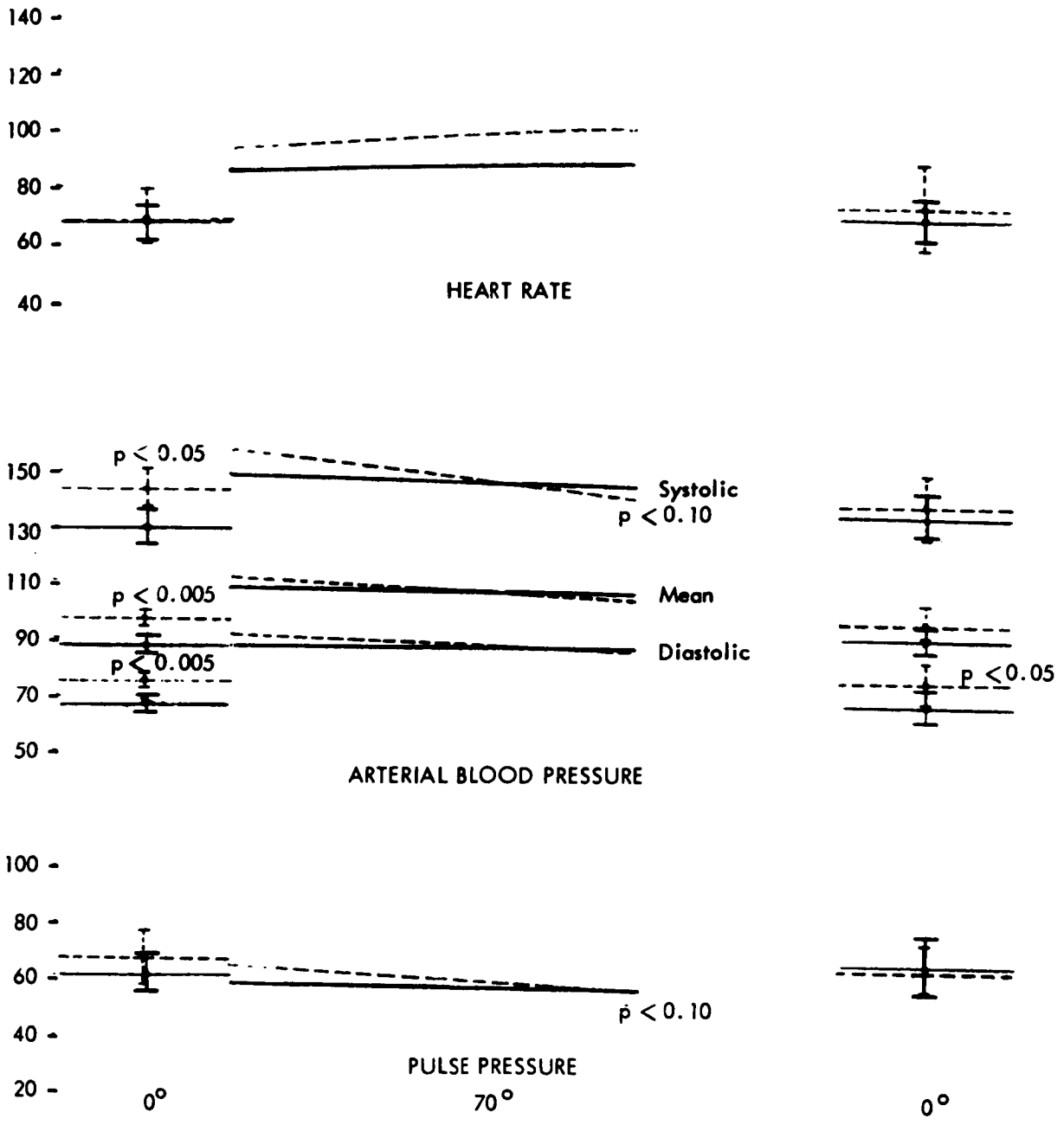


Figure 17.- Illustration suggesting that isometric exercises had a protective effect on individuals undergoing bedrest studies.

A STUDY OF THE EFFECT OF WATER IMMERSION ON HEALTHY ADULT MALE SUBJECTS: PLASMA VOLUME AND FLUID-ELECTROLYTE CHANGES

Fred B. Vogt, M.D.
Department of Rehabilitation,
Baylor University College of Medicine,
and the Texas Institute for Rehabilitation and Research,
Houston, Texas
Philip C. Johnson, M.D.
Department of Medicine,
Baylor University College of Medicine,
and the Methodist Hospital,
Houston, Texas

The total effect of prolonged periods of weightlessness on various body functions is not known. There have been observations of orthostatic cardiovascular instability and dehydration in association with two relatively short duration orbital flights of the United States (refs. 3 and 6).

Since water immersion and bedrest immobilization experiments are believed to simulate some of the conditions of weightlessness, information from such studies may be helpful to predict cardiovascular changes which may occur in association with future space flights, as well as to help interpret some of the observations made in association with an actual space flight. During water immersion (refs. 13, 9, 10, 1, 8, 19, 18, 23) and bedrest (refs. 7, 27, 21, 5, 20, 26, 22, 24, 25) experiments, a significant mobilization or redistribution of body fluids, and cardiovascular intolerance to passive tilt have been found. Experimentation has also established a relationship between orthostatic cardiovascular changes and diminished blood volume (refs. 14, 15).

Of the three fluid compartments, the intravascular fluid compartment (blood volume) directly affects cardiovascular response to passive tilting. This effect is related not only to the total volume of blood present, but also to the availability of this blood for heart filling and delivery to the peripheral arterial system. The intravascular fluid compartment is of further importance in maintaining over-all fluid balance of the body. Fluids taken into the body are absorbed and generally pass into this compartment to be transported to other fluid compartments of the body. This compartment is intimately concerned with fluid and electrolyte control and elimination mechanisms.

This paper reports on observations of plasma volume and related measurements during two 6-hour water immersion experiments. Fluid and electrolyte observations were made. Consideration is given to the relation of changes in these measurements to the cardiovascular deconditioning seen in the specific experimental test situation of water immersion.

METHODS

Four healthy adult male college students in the age range of 21 to 25 years who had participated previously in extensive bedrest studies were used as subjects. An additional subject who did not participate in the immersion studies was used as a control. Table I summarizes the subject characteristics.

TABLE I.- SUBJECT CHARACTERISTICS

Subject initial	Age (years)	Weight (kg)	Height (cm)	B. S. A.* (m^2)	Student occupation
M. A. C.**	23	65.3	177.8	1.81	Student
C. E. R.	25	84.4	192.4	2.15	Student athlete
R. S. H.	22	66.5	172.4	1.80	Student athlete
W. F. M.	23	67.5	171.0	1.81	Dental student
B. E. H.	21	70.2	177.8	1.88	Student

*From Dubois Body Surface Chart by Boothby and Sandiford

**Control subject

The subjects underwent two periods of water immersion of 6 hours duration, preceded and followed by a tilt table test. During the periods of water immersion, the subjects were immersed in a head-out position. They were allowed a minimum amount of activity in the pool, but most of the time they remained in a sitting position. Accessory breathing apparatus was not used. The temperature of the water was maintained at approximately 93° F. Immersion test number one was followed the next day be immersion test number two.

During immersion test number two, cuff-tourniquets were applied to the proximal part of all four extremities of the subjects. The cuffs were inflated simultaneously on all subjects by a single pressure bottle air source which provided a 60 millimeter mercury pressure referenced to the atmosphere. A 1-minute-on, 1-minute-off cycle was used with an inflate and deflate period of approximately 5 seconds duration. The cuffs on the lower extremities were located approximately 60-70 centimeters below the level of the water because of the posture the subjects maintained during immersion.

The subjects were immersed from 1300 to 1900 o'clock to correspond to a urine collection period that was used for a previous bedrest study on these subjects 2 months previously. During the periods of immersion, fluid intake and output were recorded carefully. Skin dry weights were obtained prior to and after immersion. The subjects were allowed to drink fluid ad libitum. They were fed after the tilt table test which immediately preceded the time of their entrance into the pool. This fluid intake was included as part of their over-all fluid intake. A malted milk was offered to them approximately 4 hours after start of immersion.

Venous blood was drawn immediately before and after water immersion for serum protein, sodium, potassium, and osmolarity. Another blood sample was drawn after 2 hours of immersion for hemoglobin and hematocrit determinations. In addition to obtaining the urine volume for the total collection period, urine was collected over the 6 hour immersion period by periodic samples to monitor changes of specific gravity. Control data on urine volume and electrolyte excretion are available from the bedrest study completed earlier on these same subjects.

Plasma volumes by a radioisotope (RISA) technique were determined immediately before and immediately after each immersion period. A pre-injection control sample of venous blood was collected for background radioactivity, after which 1 milliliter of the radioisotope solution was injected. A dual radioisotope technique was utilized in order to provide some assessment of the transfer of albumin into and out of the vascular space during immersion and during the tilt tests that followed the immersion. For the first pre-immersion plasma volume determination,

5 microcuries of I^{125} were injected. After 10 minutes mixing time, 6 milliliters of venous blood were withdrawn into a heparinized syringe. Additional samples were withdrawn 2 hours and 6 hours after the start of immersion to follow the disappearance rate of the tagged albumin. The blood collected was centrifuged and the plasma removed. Duplicate 1-milliliter aliquots of plasma were pipetted and counted in a scintillation well detector using a single channel analyzer for each determination. One microcurie of I^{131} was used in the post-immersion test of the first experiment. On the following day, the pre-immersion isotope dosage used was 10 microcuries of I^{131} and the post-immersion dosage used was 20 microcuries of I^{125}. Plasma samples were obtained for counting after each of the tilt tests.

The disappearance of radioisotope tagged albumin from the vascular compartment was evaluated by counting the radioactivity of 1-milliliter of plasma collected after water immersion for the isotope injected prior to water immersion, to give a value of "albumin counts" per milliliter of plasma. Then, the plasma volume determined with a different isotope was multiplied by this value to obtain the tagged albumin in the circulating blood volume. This disappearance or exchange of a particular tagged albumin was obtained by comparisons to measurements made at the start of the immersion period.

Hematocrits were determined by the micro-capillary technique using the heparinized blood samples and spinning the capillary tubes for 4 minutes at 11,500 rpm. Hemoglobins were determined using an alkaline-buffer method to measure oxyhemoglobin. Serum and urine sodium and potassium were determined by a flame photometer. Serum protein was determined by the method of Kingsley (ref. 17). Serum and urine osmolarity were determined immediately after collection of the samples using an "Advanced Osmometer."[1]

RESULTS

Table II presents the plasma volume determinations made prior to and after each immersion period. A plasma volume was obtained on a control subject simultaneously with the test subjects except for the one time he was unavailable for testing at the conclusion of the first immersion period. The values are presented as milliliters of plasma volume per kilogram body weight. All four subjects showed a decline

[1]Advanced Instruments, Inc.: Newton Highlands, Massachusetts.

in plasma volume in the first 6-hour period of immersion, with a mean decrease of 12 percent. The plasma volumes had not returned to control values at the start of the second test the following day. However, during the second immersion period, to which cuffs were added, all subjects showed a small increase in plasma volume.

TABLE II.- RISA PLASMA VOLUMES

(ml/kg)

	Test number 1		Test number 2	
Subject	Preimmersion	Postimmersion	Preimmersion	Postimmersion
Control	54.9		53.0	54.1
C. E. R.	52.5	44.2	49.2	51.4
R. S. H.	45.9	44.7	44.7	49.4
W. F. M.	40.2	34.3	38.7	40.2
B. E. H.	47.1	40.3	44.3	46.6
Mean	46.4	40.9	44.2	46.9

After the first period of water immersion, three of the four subjects (R. S. H., W. F. M., and B. E. H.) showed a marked drop in blood pressure resulting in syncope, and marked cardiac acceleration when they were tilted to the 70° head-up position. None of the subjects experienced syncope following the second period of immersion to which cuff-tourniquets were added during immersion, and blood pressure and heart rate changes were less marked. The response of these subjects to tilt tests performed before and after immersion is presented in detail in a separate report (ref. 23).

Radioisotope tagged human serum albumin disappearance rates from the vascular system was observed in the subjects by the use of a dual radioisotope technique, and by progressively increasing the radioisotope test dosage. For the control subject who did not undergo water immersion tests, 19 percent of the tagged albumin disappeared from the circulating plasma after 6 hours on the first day, and 23 percent on the second experimental day. For the subjects undergoing the immersion tests, on day one, the mean disappearance rate of tagged albumin was 35 percent, and on test day two (when no syncope was observed) it was 26 percent.

The changes in hematocrit, hemoglobin and serum protein during the study periods are indicated in table III. During each test period, three of the four subjects showed a decreased hematocrit after 2 hours of immersion. The hematocrit at the end of the first immersion period had essentially returned to the pre-immersion value. These changes cannot be correlated directly with plasma volume or total blood volume changes. The hemoglobin concentrations showed random minor changes during the experiment. Serum protein concentration showed small irregular changes during both immersion periods.

Table IV presents the weight changes of the subjects, the fluid intake, and the urine output during each immersion period. Control values for each person are presented as the average urine volumes passed by these same subjects for a week control period prior to the study at which time the subjects were undergoing normal activities. The minimum and maximum urine volumes excreted for the 6-hour collection periods during this control week also are indicated. The urine volumes obtained during immersion are somewhat higher than the average control, but the range of volumes for the control days makes it difficult to describe a true water diuresis from this data, and the specific gravity of the urine did not change significantly during the experiments. The subjects did not complain of thirst. Urine sodium, potassium, and osmolarity for pooled 6-hour samples collected on each subject for the two immersion periods showed no significant or consistent change that differed from control data collected on these subjects previously.

TABLE III.- HEMATOCRIT, HEMOGLOBIN, SERUM PROTEIN

		Test number 1			Test number 2		
Subject	*	Hematocrit, percent	Hemoglobin, gm-percent	Protein, gm-percent	Hematocrit, percent	Hemoglobin, gm-percent	Protein, gm-percent
C. E. R.	Pre	43.5	12.7	7.4	44.5	11.9	7.6
	2 hr	43.5			42.5		
	Post	44.0	12.9	6.9	43.5	11.8	7.3
	P. Tilt	45.5			46.0		
R. S. H.	Pre	48.0	14.0	6.8	48.0	13.0	6.8
	2 hr	46.5			44.0		
	Post	47.0	13.8	7.1	45.0	12.8	7.1
	P. Tilt	47.0			45.0		
W. F. M.	Pre	48.0	12.5	8.1	47.0	12.2	7.9
	2 hr	45.0			45.0		
	Post	48.0	13.0	8.1	46.5	12.4	7.4
	P. Tilt	46.0			48.0		
B. E. H.	Pre	44.0	12.3	7.2	44.5	11.8	7.0
	2 hr	43.5			46.0		
	Post	44.0	12.0	7.4	43.0	12.1	7.2
	P. Tilt	48.0			46.0		

*Pre (Preimmersion)
Post (Postimmersion)
P. Tilt (Post-Tilt)

TABLE IV.- ORAL INTAKE - URINE OUTPUT DURING WATER IMMERSION

		Test number 1			Test number 2		
Subject	Control, (ml)*	Intake, (ml)	Output, (ml)	Weight change, (kg)	Intake, (ml)	Output, (ml)	Weight change, (kg)
C. E. R.	200 290 560	1200	900	-0.2	1160	530	+0.3
R. S. H.	220 295 385	800	510	-0.1	1500	190	+0.9
W. F. M.	270 500 770	800	390	-0.2	1300	360	+0.6
B. E. H.	195 412 770	1000	760	0.0	1500	620	+0.3

*One week control on each subject during normal activity, giving average urine volumes with minimum and maximum values for these periods above and below the average value.

Table V presents the serum sodium, potassium, and osmolarity measurements made before and after each period of immersion. There are no distinct trends of change or differences before and after immersion, except for the serum osmolarity of R. S. H., which changed from 295 mOs/kg to 303 mOs/kg during the second immersion period.

TABLE V.- SERUM MEASUREMENTS

		Test number 1			Test number 2		
Subject	Immersion	Sodium, meq/L	Potassium, meq/L	Osmolarity, mOs/kg	Sodium, meq/L	Potassium, meq/L	Osmolarity, mOs/kg
C. E. R.	Pre	151	4.8	294	146	4.1	300
	Post	151	4.4	299	151	4.1	297
R. S. H.	Pre	145	4.3	296	147	3.8	303
	Post	147	4.4	296	147	4.4	303
W. F. M.	Pre	147		296	145	4.9	296
	Post	152		297	148	4.7	297
B. E. H.	Pre	141	4.3	296	146	4.6	293
	Post	145	4.7	295	146	4.5	297

DISCUSSION

Our observation of an apparent hemodilution as shown by the hematocrit changes during the early phase of the water immersion periods, and a decrease in the plasma volume at the end of the 6-hour immersion period confirm the observations related to this measurement made by others (refs. 9, 10, and 11). Considerably more success was found in this experiment using radioisotope dilution techniques than was reported by McCally (ref. 18), and the consistency of response of the plasma volume measurements on the control subject adds further support to this reliability. The plasma volume decrease may be related to the decreased tolerance to tilt noted in these subjects. However, it does not seem to be responsible for the entire spectrum of changes observed.

Green et al (ref. 14) describe two dominant types of reactions to tilt after acute blood loss. When the blood loss does not exceed 14 milliliters per kilogram, Green reported that the response to tilt was characterized by a brisk cardiac acceleration with the usual systolic drop and the diastolic rise in blood pressure seen with tilting normal subjects. Cardioacceleration in the range of 20 beats per minute was found when 9 to 14 milliliters per kilogram was withdrawn. Occasionally they found a second type of tilt response characterized by marked tachycardia, air hunger, faintness, and a rapid fall in blood pressure to shock levels similar to the changes seen in the subjects in the water immersion experiment during which cuffs were not used. Green et al (ref. 14) noted a progression from the first type of reaction to the second type in the subjects as blood was withdrawn progressively.

Our failure to observe a significant diuresis with water immersion is comparable to the findings observed by Benson et al (ref. 2), but other investigators (refs. 9, 10, 1, 11, and 12) have described a diuresis rather consistently. It is possible that a diuresis would have been observed in these subjects if they had been exposed to a longer period of immersion. Our data suggest that a significant and brisk diuretic response, with an associated intense thirst and change in body weight and possibly the vascular volume, no longer can be implicated as the initiating factors in the progression of events leading to the more severe tilt table intolerance seen after these water immersion experiments. Our failure to note a significant change in weight and in serum sodium, potassium, protein, and osmolarity, associated with definite plasma volume change suggests fluid-electrolyte-protein shifts out of the vascular compartment as one of the contributing causes of the intolerance to tilt after the first immersion period without cuffs.

Some estimate of the magnitude of the fluid and protein shift is available from the albumin disappearance study. Thirty-five percent of the circulating radioiodinated albumin disappeared during 6-hours of immersion. This was greater than the 19 percent seen in the control subject and the 26 percent of the test subjects following the immersion period to which cuffs were added. The disappearance rate of the control subject and the test subjects on the second day corresponds to the expected decay rate (refs. 4 and 16). Since there was no significant change in serum protein concentration associated with the disappearance of the radioactive albumin, the data suggests a shift from the circulating vascular space of an electrolyte-water-protein combination to the extravascular compartment.

The drop in plasma volumes seen in these studies (about 6 ml per kg) was associated with tilt responses of the type seen by Green with a much larger loss of blood and plasma. If response to tilting in the two situations can be compared, one must consider more complicated mechanisms responsible for the observations seen in this water immersion study. The increased disappearance rate of albumin from the vascular space suggests the possibility of erroneously high values for the plasma volume determined after immersion if there is a correspondingly more rapid loss of tagged albumin during the ten minute mixing period. A poor correlation of the hemoglobin and hematocrit changes with the RISA plasma volume changes could result if the venous samples are not representative of the total circulating blood volume, especially in this acute experiment in which there appear to be alterations in the fluid-electrolyte-protein and plasma volume control mechanisms.

Any theory of the mechanisms involved in the tilt table intolerance also must consider the redistribution of the circulating blood volume seen in this study as well as pooling of blood due to loss of venomotor tone. Such changes could have resulted from the exposure to the relatively high water temperature. The protective action seen with the cuffs is still to be explained.

The preliminary observations presented here are presented to provoke new thoughts as to the possible physiological mechanisms for the condition called "cardiovascular deconditioning" seen with water immersion. An understanding of these changes can be learned only from further studies. Further, it is too early to imply that common mechanisms of action are responsible for the cardiovascular deconditioning of bedrest, chair rest, space flight, and water immersion.

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THE ERKIN TESTS AND EXERCISES

By Willis C. Beasley, Ph.D
Associate Professor, Baylor University College of Medicine

INTRODUCTION

Unfortunately, for the objectives of this conference, conclusions on the effects from exercise in preventing or reducing physiological deconditioning resulting from prolonged bedrest in our 1964 research study cannot be reported today. We are in the midst of data tabulation and analysis at the present time, and interpretations on the treatment effects will not be available for several months. Consequently, my presentation will be limited to a description of the exercises and tests that were used and how they relate to the total experimental design.

The choice of exercise, in relation to the space program, does involve a great many considerations, and I took the time this year to study the problems from the standpoint of the NASA requirements with the intention of designing an exercise program which could be utilized also in the Gemini capsule. Therefore, I conferred with staff members of NASA. Also, I came out to the MSC grounds at Houston and crawled into the capsule, and tried to get the feeling of what the astronaut is faced with: how much mobility he has; and how he can produce muscular effort in the situation. From this I devised some exercises for the bedrest study which could be transferred to the capsule situation. Also, the personnel at NASA had made some progress in devising an exerciser and, even though I have a great many exercise facilities at TIRR, I decided to utilize the basic device NASA had already started because this was another part of the practical consideration.

THE ERKIN PROGRAM

To the program of exercise, which I developed and supervised, the name "Erkin" was given. This designation was improvised as an abbreviation from "ergonomics" and "kinesiology" as a brief label, which is used also as a coding category for processing of data.

The Erkin program is divided into two aspects: (1) criterion tests, designed to evaluate strength level, endurance, and cardiovascular response to this form of stress test; and (2) conditioning exercises, intended to aid in the prevention of general physiological deconditioning associated with confinement to bed for a protracted period of time. The schedule of the various Erkin tests and exercises is listed in the master protocol. A brief summary is provided here of the purpose and procedure for each Erkin protocol as used throughout this study.

Requirements

The objectives of the bedrest studies were reviewed in detail prior to devising these Erkin tests and exercises. Restrictions upon the form of the proposed exercise resulted from the limitation in the range of motion of the arms (elbow flexion) and the short range of extension allowable at the knee joint. The exercise procedure was designed so that it could be used by astronauts in the Gemini space capsule. The conditioning exercises were developed, therefore, around a pattern of isotonic motion of limited range.

THE BUNGEE EXERCISER

The device employed for conditioning exercises is called a bungee, since the load is produced by the stretch imposed upon two strands of bungee rubber such as that used in underwater spear guns. The initial model of this exerciser, provided by NASA, was modified to adapt the primary model more effectively to this study program.

In order to have predictable and measured loads or exercise doses for each individual subject, the bungee strands were carefully calibrated by applying known weight loads and measuring the stretch produced. Calibration curves were derived from these data for all bungee strands employed in the exercisers. Also, several strands were repeatedly stretched and relaxed up to 5000 times to determine durability and retention of elasticity. The exerciser units were then assembled in a manner to permit adjustments in load and range for individual subjects.

ERKIN 1 PROTOCOL (DESIGN MEASUREMENTS)

This series of tests was designed to provide information on the individual's maximum pulling force at different points in the range of

motion in a manner adapted to the bedrest situation. The subject was positioned supine, with feet braced against a footboard. One end of an adjustable but nonyielding cable was attached to the footboard and the other end was fastened to a bar handle, which is grasped by the subject with both hands. A tensiometer is coupled in the cable line to register the axial force produced along the cable by the subject's pull. Measurements were taken with the arms in full extension, with the elbows flexed to 45°, and finally with the elbows flexed to 90°. Measurements were taken also of the distances between the handle and the footboard for each subject in each of these positions. These values are then used to design the lengths and degree of bungee stretch for each subject's exercise dose.

ERKIN 2 PROTOCOL (STANDARDIZATION TESTS)

This series of tests was designed to standardize in advance the exercise dose for each subject. The objective of adjusting the exercise dose is to avoid severe fatigue while still obtaining moderate but not excessive cardiovascular response to the exercise, as measured by the increase in the heart rate during the exercise. It was decided to assign arbitrarily an exercise dose that would increase the heart rate 40 to 50 percent over the resting level in a two-minute exercise of 120 pulls on the bungee at the rate of one pull per second.

Initially, each subject was given a dose of bungee pulling at 40 percent of his maximum in the range of motion terminating at 90° elbow flexion. All subjects are to use the same length of bungee rubber, with a variation in the length of the coupling cable to the foot piece made according to the height of the subject. The starting point for the pull is determined by the magnitude of bungee stretch at this terminal tension. During this run, the ECG was monitored. If this exercise was found to be too severe (i.e., produced excessive increase in heart beat rate), the terminal tension was reduced and another run was monitored. If the initial exercise was too easy, the terminal tension was increased until a desired increase in heart rate was achieved. In this manner a standard exercise dose and bungee setting were determined in advance for each subject prior to the first bedrest period. This dose was retained for each man for the in-bed conditioning exercises, which were designated as the Erkin 5 protocol.

ERKIN 3 PROTOCOL (CRITERION TEST)

This test was designed to reveal the subject's condition and changes from time to time in respect to strength level, endurance

(or fatigability), and response of the heart rate to 50 percent of maximum exercise and a maximum exercise series. The sequence is standardized for each subject. This test was given before and after each bedrest period and several times between. It was used throughout the whole study as a criterion of changes in these particular functions. This test was given to each subject also on the last day of each bedrest period (the day preceding tilts) with the standing phase omitted. The following was the standard sequence employed in Erkin 3 while tensive force of each pull, the electrocardiogram, respiration, and blood pressure were monitored:

1. Subject stands 1 minute.

2. Subject lies supine, and gives two maximum pulls on the tensiometer cable, arms at full extension.

3. Subject rests quietly 4 minutes.

4. Subject pulls 15 times, 5 seconds on, 5 seconds rest, on cable tensiometer at 50 percent of his maximum by observing meter that shows his achieved force of pull.

5. Subject rests quietly 5 minutes.

6. Subject pulls 15 times, 5 seconds on, 5 seconds off, on cable tensiometer at maximum effort.

7. Subject rests quietly 5 minutes.

8. Subject stands 1 minute.

ERKIN 4 PROTOCOL (EXPERIMENT)

Time variation of Erkin 2, used as a special experiment, but not as part of the bedrest study evaluations.

ERKIN 5 PROTOCOL (CONDITIONING EXERCISE)

This is the standard in-bed exercise routine used throughout the study for individuals (or groups) for whom exercise was prescribed in the design. The dose used for each individual is that standardized in the Erkin 2 series, and remained the same throughout. Each subject had his own bungee exerciser.

These exercises were performed simultaneously by all subjects for whom exercise was prescribed in the master protocol. The routine was repeated ten times daily, at hourly intervals throughout the ten-day bedrest period, beginning at approximately 8:00 a.m.

The exercise routine was as follows: 120 pulls on the prescribed bungee at the rate of one pull per second, that is, an exercise period of 2 minutes.

This standard routine was interrupted slightly once per day during the bedrest period for ECG monitoring. The routine was also monitored with ECG twice before and twice after each bedrest period. For this set, each individual was tested sequentially, and the ECG was monitored 2 minutes before the exercise, at all times during the exercise, and 4 minutes after the exercise. This monitoring once daily was done also for subjects not on the exercise schedule. During the control bedrest period when no subjects were on exercise, Erkin 5 was given once every 2 days to all subjects as a criterion test.

ERKIN 6 PROTOCOL (CRITERION TEST)

This test was performed with the bungee exerciser and is the same as Erkin 5 except that the ECG is monitored 4 minutes before exercise and 5 minutes after exercise. The exercise routine is 300 pulls on the bungee at a 1-second cadence, with a 5-second rest pause at the end of each 30 pulls. The Erkin 6, therefore, comprised a 5-minute version of the 2-minute Erkin 5 routine. The purpose of this test is to evaluate response to a more prolonged exercise than that provided by Erkin 5. Erkin 6 was given before, after, and midway through bedrest periods.

STUDY PERIODS

The design of the bedrest study comprised seven periods. During four periods, all subjects were "mobile," that is, out of bed and carrying on usual activities. During the initial "mobile period," which was the 10 days prior to the first bedrest period, evaluations and experimental tests were performed. The final "mobile period" lasted 7 days after the third bedrest period. In between the 3 bedrest periods, 2 "mobile periods" of 22 days each intervened. There were 3 bedrest periods of 10 days each.

SUBJECT GROUPS

Ten subjects were studied in detail. They were divided into two groups, A and B, for the purpose of alternate treatments. The three treatments applied during the bedrest periods included (a) Erkin 5 exercises, (b) venous occlusion cuffs applied to lower extremities, and (c) bedrest only with neither (a) nor (b). These treatments were applied alternately to Groups A and B as follows:

	Bedrest I	Bedrest II	Bedrest III
Group A	Cuffs	Exercise	Neither
Group B	Exercise	Cuffs	Neither

ERKIN TESTS AND EXERCISES PERFORMED

The schedule of the Erkin tests and exercises actually performed during the seven study periods by the two groups of subjects were as follows:

Study Period	Erkin Protocol	Number of Times Performed Group A	Group B
	1	2	2
	2	2	2
1	3	2	2
Mobile	4	1	1
7 days	5	2	2
	6	3	3
2	5	10 times daily	1 time daily
In bed	6	1 tenth day	1 tenth day
10 days	3	1 tenth day	1 tenth day
3	3	4	4
Mobile	5	3	
22 days	6	3	3

Study Period	Erkin Protocol	Number of Times Performed Group A	Group B
4	5	1 time daily	10 times daily
In bed	6	1 tenth day	1 tenth day
10 days	3	1 tenth day	1 tenth day
5	3	6	
Mobile	5	4	
22 days	6	4	
6	5	1, 3 different days	1, 3 different days
In bed	6	1 tenth day	1 tenth day
10 days	3	1 tenth day	1 tenth day
7	5	2	2
Mobile	6	2	2
6 days	3	3	3

The measurements obtained through applying the various Erkin tests and exercises, combined with the measurements on cardiovascular and pulmonary responses to the exercises at the time they were performed, provide a relatively large field of information on the effects from the treatment cycling as described previously. Figure 1 shows one plot of data depicting heart rate response to the Erkin 3 exercise by one subject, simply to give an example of the information detail available from one test. The figure is indexed clearly so the reader can interpret the information shown in detail. There were 180 tests of this Erkin 3 given to the 10 subjects, so that a number of plots like this one have been produced from the IBM cards on this one pattern of exercise. In addition, there are 140 plots of the Erkin 6 exercise. There are 1140 records of the Erkin 5 conditioning exercise. These are the basic programs of tests that will yield significant basis for interpreting possible effects from bedrest of 10 days' duration (with or without concomitant venous occlusion cycling, Erkin 5 exercises) on cardiovascular deconditioning, muscular strength, and fatigability. The details of the analysis are too complex to be reviewed here. The total program of this analysis, however, is designed to bring out evaluation of effects on these several processes. The main message to leave with you now is that the kinds and numbers of measurements made should be entirely adequate for a firm conclusion relative to the

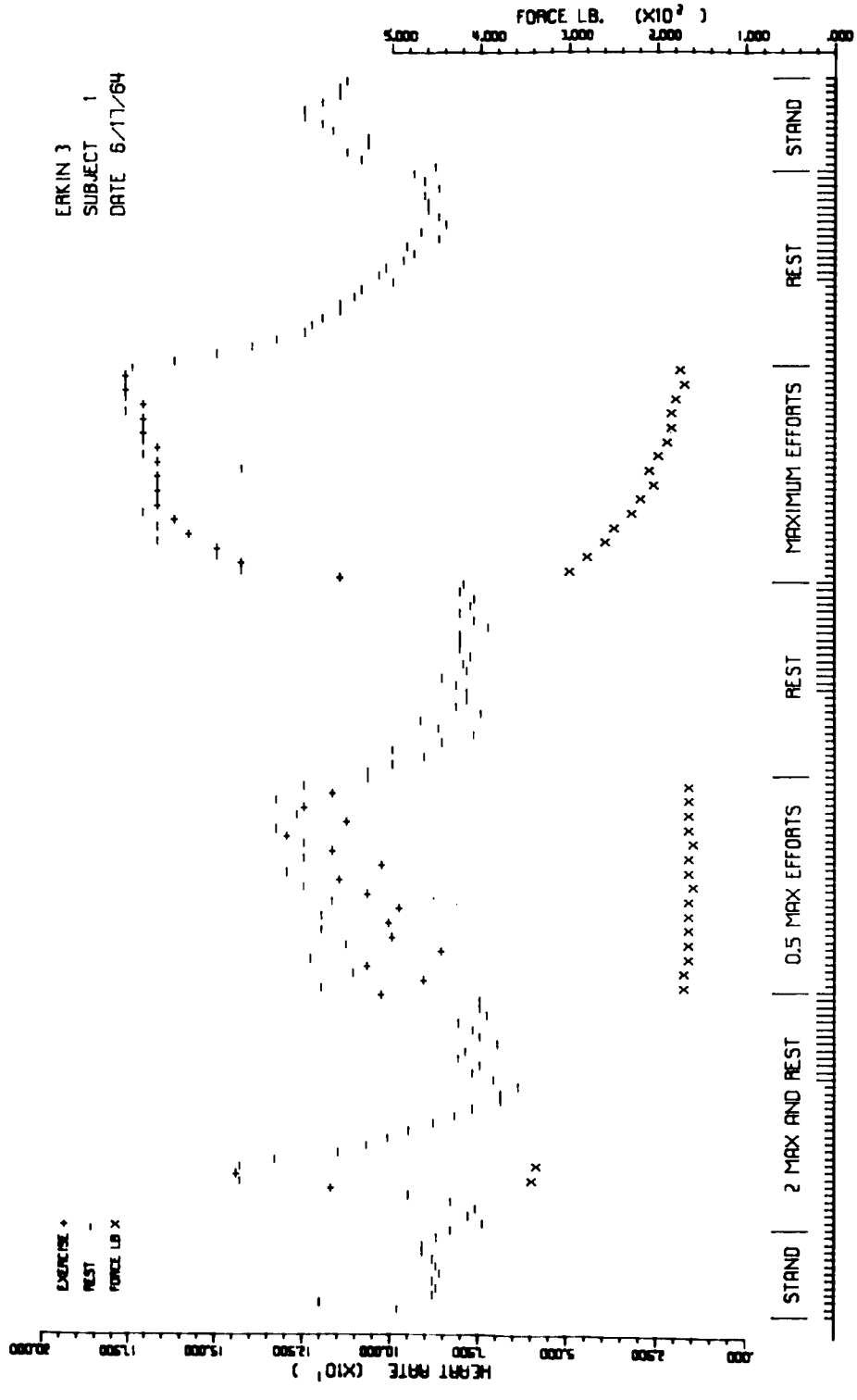

Figure 1. Data plot showing heart rate response to the Erkin 3 exercise by one subject.

effectiveness of exercise of the type employed in reducing deconditioning during bedrest periods of the duration employed in this study. Whether or not the amount of exercise itself as used here is adequate we do not know, and cannot know, except through extended comparative experimental studies.

CIRCADIAN DYSRHYTHMIA AND HUMAN PERFORMANCE

By Harry Lipscomb, M. D.
Baylor University College of Medicine

Rhythmicity of function appears to be an inherited characteristic of all biological material on this earth. The earliest observations of such rhythms of which we have complete recorded information dates to the middle of the eighteenth century when the French astronomer De Marian described rhythmic daily movements of plant leaves, as recorded by a crude kymograph. During the next 250 years, the literature has become replete with descriptions of biological rhythmicity in every known genera and species, from plant and animal unicellular organisms up to whole organ systems including man. Additionally, the types of rhythms have encompassed every conceivable area of biochemistry, motor-function, and morphologic growth.

From rhythmic leaf movements of plants to inter-tidal migration and color change in Crustacea to daily fluctuations in electrolytes in man, rhythms have been described in virtually every measurable biological process. Additionally, it is important to note that the character of these rhythms has invariably possessed a striking correlation with external geophysical events, most notably solar or lunar cycles possessing generally a period of twelve or twenty-four hours. Indeed, so precisely synchronized do these rhythmic biological events seem to be to external events (primarily, day-night cycles) that they have been termed diurnal, nychthermal, or endodiurnal rhythms.

Classic descriptions of rhythmic phenomena in plants and animals over these years have generally been restricted to short-term series of observations with little or no attempt to interpret the underlying mechanisms generating such rhythmic behavior. The earliest and apparently most logical explanation for such events was that from a teliologic standpoint rhythmic events existing in biological life were triggered and entrained and synchronized with the day-night cycle. Two points, however, mitigate against this as a totally valid hypothesis, the one being that such rhythms are seen to persist even after day-night cycles are abolished or exist in blind individuals, and the more recent observation that rhythms under certain circumstances do not possess the precise 24-hour period, but rather periods somewhat shorter or somewhat longer than precisely 24 hours. In fact, this latter observation prompted the coining of the term circadian which means "about a day,"

to suggest that the rhythms were not precisely 24 hours in length. The observation of the persistence of rhythms under constant conditions and the presence of persistence of rhythms with periods longer or shorter than our customary geophysical day-night cycle has led several observers to believe that some form of endogenous clock-mechanisms must exist which may modulate or at least integrate external signals coming from our terrestrial environment.

The time has now come, therefore, to go from simple observation of the phenomena to an investigation in depth of the mechanisms underlying biological rhythmicity. This is particularly important in terms of the manned space effort for the following reason. Recent observations on humans displaced by jet travel rapidly across time zones east-west or west-east suggest that such displacement abolishes these rhythms for a period of several days, and during this period of abolition of rhythms, human performance of discrete sensory-motor tasks is seriously impaired. The questions which we might pose here, therefore, are whether or not such rhythmic behavior in biological and metabolic functions are tantamount to efficient human performance, and whether or not, under conditions of extra-terrestrial flight, we might lose useful external time givers, thereby suffering impairment of performance. If such proves to be the case, it may well be worthwhile that we consider providing rhythmic exteroceptive cues in order to maintain rhythmic biological functions, and thereby performance. Furthermore, we would like to know, if these rhythms prove to be exogenous in nature, whether or not an heirarchy of external clues exists, such as, whether light, then temperature, then humidity, then barometric pressure act as sequentially important time givers to human biological rhythms and whether an heirarchy exists in the rhythms themselves. For instance, whether or not rhythmic secretion of pituitary adrenal hormones might be critical whereas body temperature might be rather unimportant to adequate performance. These then are the major questions which we would like to answer in our own study of rhythms, and to which we are currently addressing our efforts.

Towards this end, we are currently undertaking for the National Aeronautics and Space Administration a series of experiments conducted within the Texas Medical Center at the Baylor University College of Medicine designed to study rhythmic biological, biochemical, and physiologic events in normal humans, alter these rhythms by subtle manipulation of the external environment (light, duration) and assess the ability of the subjects discrete sensory-motor tasks of vigilance, time-perception, and other coordinated hand-eye movements. In such an environment, we intend to place subjects for protracted periods of time and subject them to the environment of altered lighting situations, simultaneously measuring several parameters of physiologic function (blood pressure, pulse, respiration, temperature, EKG, EOG, EEG), parameters of biochemical function in urine (electrolytes, steroids, and catechol amines), and discrete

parameters of sensory-motor performance (time-perception, judgment, problem-solving, radar-tracking, vigilance). Subjects confined to this chamber will be given no external clues as to time of day or night; and in such a chamber, time disorientation poses as the only major sensory deprivation imposed upon the experimental subjects.

In the establishment of a laboratory capability for the performance of these biochemical determinations, we are presently prepared to offer to other NASA contractees laboratory facilities for the performance of a number of biochemical, biological assay, and pharmacologic determinations on body fluids, which are enumerated in Appendix 1. It is hoped that the participants in this symposium will avail themselves of the opportunity to utilize these laboratory facilities and particularly, to collaborate in projects of interest and importance to the study of human systems in relation to space exploration.

APPENDIX I

CIRCADIAN SYSTEMS LABORATORIES
BAYLOR UNIVERSITY COLLEGE OF MEDICINE

The laboratory facilities of Baylor University College of Medicine are sponsored jointly by the National Aeronautics and Space Administration and the National Institutes of Health, United States Public Health Service, and are under the direction of Dr. Harry S. Lipscomb, Associate Professor of Medicine and Physiology. These facilities have been in operation for the past 14 months, and are now equipped to handle large numbers of specimens submitted by the various MSC-NASA contractees, and related participating groups.

The present philosophy embodies the concept of handling many specimens daily, on which a relatively limited number of determinations are performed. Since the major project-oriented work of the laboratory concerns itself with fluid, electrolyte, and endocrine abnormalities related to disruption of circadian systems, the present capacity is equipped to perform on Plasma:

Na^+, K^+ } flame photometry

Cl^- titration

Epinephrine Nor-epinephrine > Weil-Malherbe-Bone

Osmolality > cryoscopy

17-OH-Corticosteroids > Porter Silber

ACTH → bioassay in hypx. rat (Lipscomb)

MSC → Shizume-Lerner-Fitzpatrick (frog-skin)

Aldosterone - double-labeling

Vasopressin (Antidiuretic Harmone) ETOH-hydrated rat - antidiuresis

Renin → (Angiotensis) - Helmer

and on Urine:

Na^+, K^+ } flame photometry

Cl^- potentiometric titration (Buchler-Cotlove)

Osmolality > cryoscopy

Creatinine > Jaffe

Ephinephrine, Nor-epinephrine } Weil-Malherbe-Bone

17-OH-Corticosteroids { Porter-Silber Reaction / Peterson-Wyngarden Modification

For the proper collection and submission of samples, we would ask that the following instructions be closely followed: For plasma or serum it is imperative that samples be quickly centrifuged, and plasma or serum be removed immediately. Additionally, such samples must be frozen immediately. Since it is impossible to do electrolytes on plasma which has been properly prepared for catechol amines (Epinephrine and Nor-epinephrine) these samples must be submitted separately. Hemolysis is to be avoided. Sodium free heparin is the anticoagulant of choice if it must be used (we prefer Na, K, Cl^-, Osmolality on serum).

For 17-OH-Corticosteroids, either plasma or serum may be used. Here, prompt removal of plasma or serum from the packed cells is imperative.

For plasma epinephrine and nor-epinephrine, a separate sample must be obtained from that for electrolytes, and the following precautions must be employed:

1. Rinse syringe with anticoagulant solution (EDTA + $NA_2S_2O_3 \cdot 5H_2O$.

2. Put 5 ml of anticoagulant in a 50 ml centrifuge tube.

3. Draw 20 ml of blood and put immediately into anticoagulant. Invert the contents gently, note the total volume (V_B).

4. Remove a sample for the determination of the hematocrit (H).

5. Centrifuge the remainder for 30 minutes at 1000 RPM. Separate the plasma and measure its volume (V_P).

6. Add an equal volume of NA acetate solution, and adjust the pH to 8.4 by continuous addition of 0.5N NA_2CO_3.

For urine, it is sufficient that all urine be collected into chilled bottles containing concentrated, analytically pure H_2SO_4, 5.0 cc/24-hour collection period. On such urine, it is possible to do, simultaneously, all of the determinations described above.

For both urine and plasma or serum, specimens must be quickly frozen as soon as possible, and shipped in dry ice, air express, prepaid, to:

Dr. Harry Lipscomb
Baylor University College of Medicine
Circadian Systems Laboratories
1200 Moursund Blvd.
Houston, Texas 77025

BASIC CARDIOVASCULAR-RENAL STUDIES

Walter H. Abelmann, M.D.
Harvard Medical School

Dr. Larry Early and myself are with the Thorndike Memorial Laboratory at Boston City Hospital. We hope that we can contribute to the areas that are of interest to the Manned Spacecraft Center. We are engaged in an effort to look at nature's experiments in terms of disease so that the exploration of possible interrelationships between blood volumes, blood flow, excretion of water and sodium in relation to possible volume receptors sensitive to distention of certain anatomical parts in the chest can be made.

First, I shall present some background work that was done, which may have some bearing on these relationships. Then, some preliminary examples of the type of studies, which we hope to do with patients. Dr. Early will address himself more to the role of the kidney, and particularly to its regulation of salt and water.

First, I will discuss some studies that Dr. Martin Duke and myself made in recent years on patients with chronic anemia (see fig. 1). We were interested in the question: "To what extent is the high cardiac output state in chronic anemia, which has been found in some and not in other patients, an obligatory one, and what possible mediators might there be?" By setting up our investigation in such a way that we studied the same patients with chronic anemia before and after treatment, we found that cardiac index consistently fell after treatment. Thus, we have come to the concept that a high cardiac output in the presence of anemia represents an obligatory response, even if in any one individual the output falls within the normal range. Blood pressure in chronic anemic patients fell within normal limits, but if we compared the blood pressure of the individual to his own blood pressure after recovering from anemia, he was relatively hypotensive when anemic (fig. 2). Total blood volume in the anemic state was relatively smaller than after treatment. Central blood volume, which is known anatomically as hard to relate to anything but was measured the same way in the same patients, showed no consistent response to treatment. If, however, central blood volume is expressed as the ratio to total blood volume, then there was a consistent decrease of this fraction. Here is a suggestion, then, of a relationship between the proportion of blood in the center of thorax and the level of cardiac output.

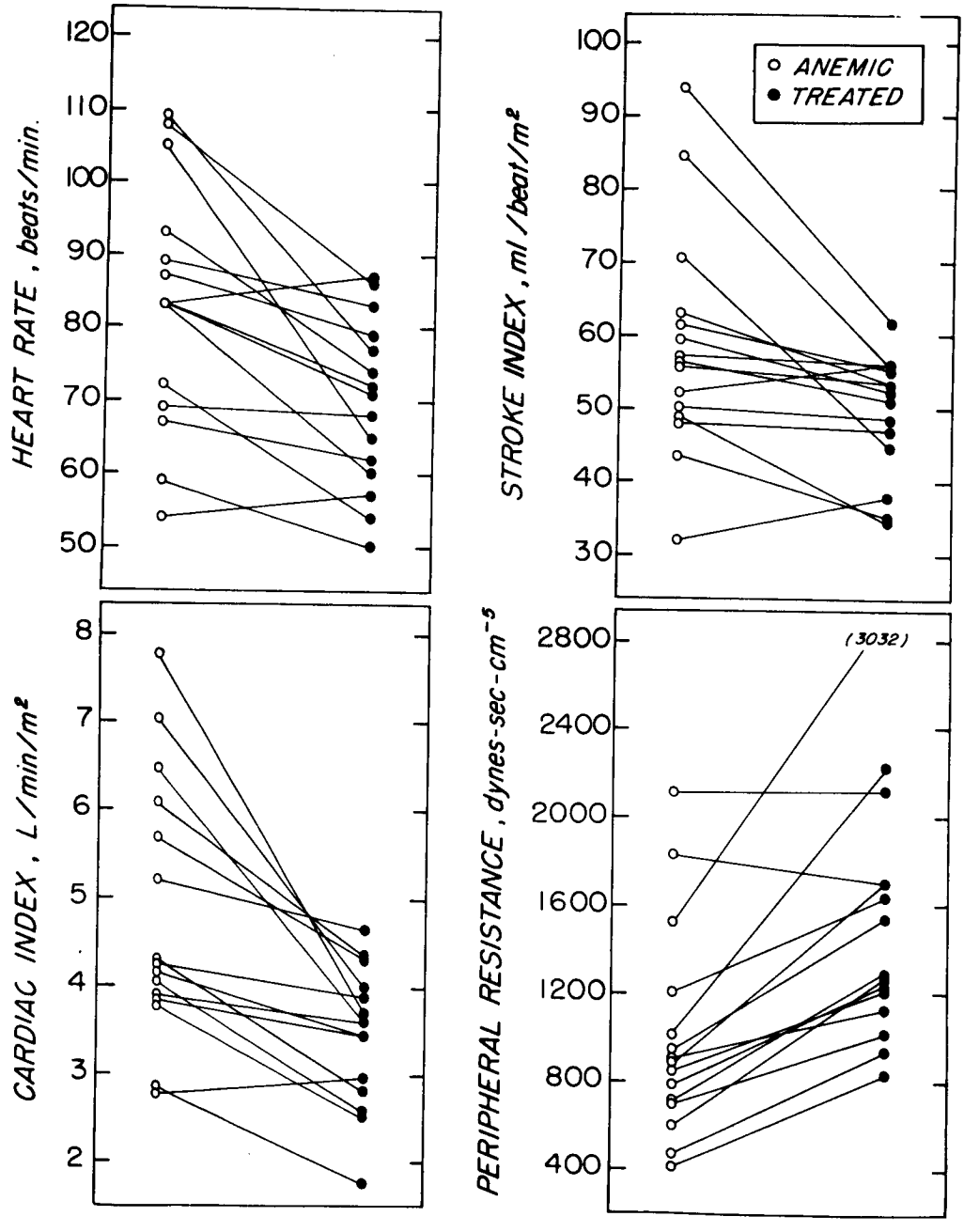

Figure 1.- Illustration showing cardiac index, heart rate, peripheral resistance, and stroke index.

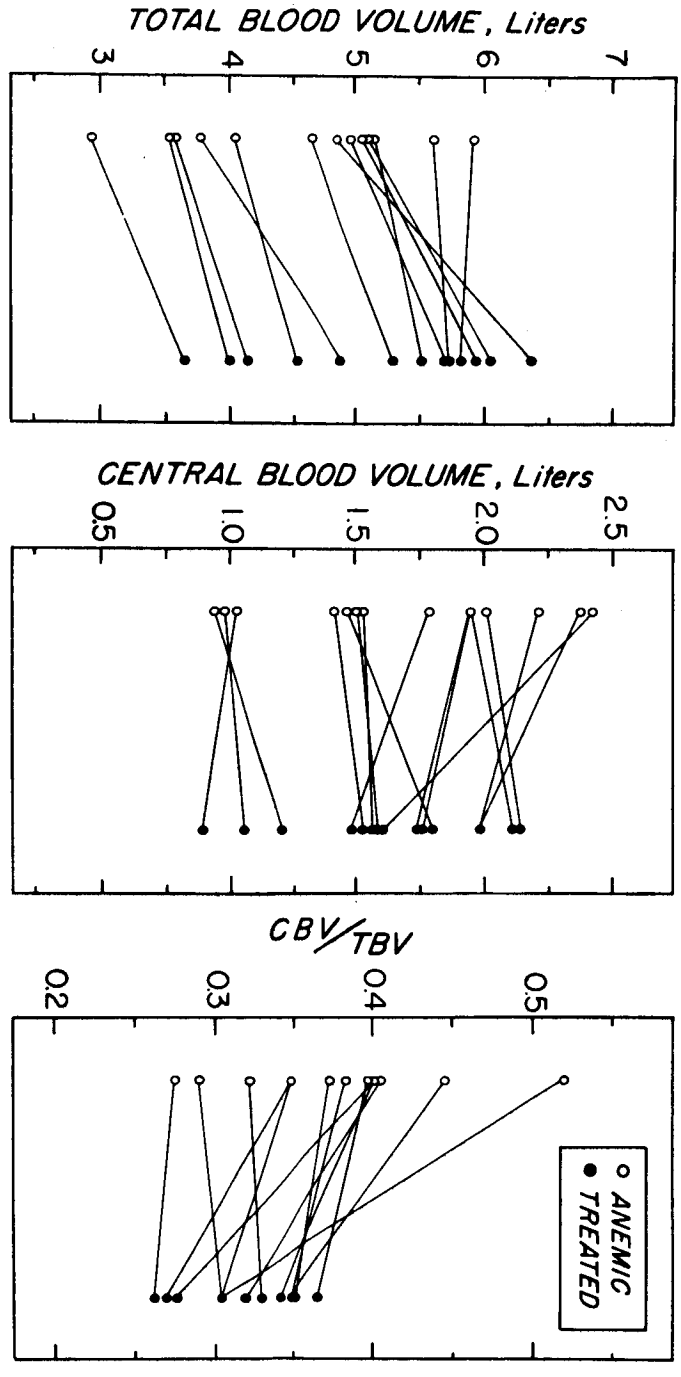

Figure 2.- Illustration showing total blood volume, central blood volume, and central blood volume over total blood volume.

In keeping with this is the response to change in posture as studied in four anemic patients (table I). Sitting up was accompanied by a 23 percent decrease in cardiac index and by a 22 percent decrease in central blood volume. Thus the high output state of chronic anemia, although obligatory, is not fixed, but does respond to changes in position.

TABLE I.- HEMODYNAMIC EFFECTS OF CHANGE IN POSTURE IN ANEMIA

(N = 4; MnHb = 5.0 gm percent)

		Supine	Sitting	Change, percent
HR	b/min	85.3	93.8	+10
CI	$L/min/M^2$	4.5	3.4	-23
SI	$ml/b/M^2$	53	38	-28
TBV	L	3.4	3.1	-7
CBV	L	1.2	0.9	-22
$\overline{BAP}$	mm Hg	77.3	96.5	+25
TSR	$d\text{-}sec\text{-}cm^{-5}$	993	1624	+64

Now let us go to a completely different area. For the past 2 years my associates and myself have been interested in asking ourselves, "What is the response of the circulatory system to acute infections, particularly acute pulmonary infections?" Our studies were stimulated by clinical observations of patients with acute pneumonia, who tolerated the pneumonia poorly, raising some question of circulatory overload. In the acute stages of pneumonia, we had expected to find, at least in some patients, a high output state, and perhaps some instances of subclinical high output failure; and in some patients a hyperkinetic response was found. Table II presents data obtained in seven patients who responded to acute pneumonia by having a high cardiac output with a normal or narrow arterio-venous oxygen difference. However, we were surprised that more frequently than the normal or high output response to pneumonia, we encountered what we have called a hypokinetic response.

TABLE II.- HYPERKINETIC RESPONSE TO ACUTE PNEUMONIA IN 7 PATIENTS

		Acute	Convalescent
H.R.	b/min	103	84
S.V.	ml/b	69	63
C.O.	L/min	7.2	5.2
A-V O_2 - Diff.	Vol. %	4.0	4.7
$\overline{BAP}$	mm Hg	82	99
T.S.R	d-sec-cm^{-5}	108	1647

Table III presents mean values of six patients with a hypokinetic response. The acute state is compared to the convalescent state: the cardiac output is low, the arterio-venous oxygen difference is wide, and the total systemic resistance, previously shown in hyperkinetic patients was low as might be expected in the presence of fever and increased respiratory work, and is high. In the absence of any change in blood pressure, this suggests vasoconstriction.

TABLE III.- HYPOKINETIC RESPONSE TO ACUTE PNEUMONIA IN 6 PATIENTS

		Acute	Convalescent
H.R.	b/m	99	94
S.V.	ml/b	52	76
C.O.	L/m	4.8	7.1
A-V O_2 - Diff.	Vol. %	6.4	4.0
$\overline{BAP}$	mm Hg	85	85
T.S.R.	d-sec-cm^{-5}	1435	1061

Now I want to show one specific patient that was recently studied with Dr. Akbarian, who illustrates some of the possible further studies that might be pursued (fig. 3). This was a 62 year old man who had suffered some rib fractures on the left 5 days before we studied him and who subsequently developed first left and then bilateral pneumococcal pneumonia. At the left base, there is an artifact and note the normal cardiac size. At the time of the first study (table IV), the man was in the hypokinetic group: he had a relatively low cardiac index - he was in acute respiratory distress and had a wide arterio-venous oxygen difference and, yet, a perfectly normal right atrial pressure. The peripheral resistance was high and the blood volume was low, as was the ratio of central blood volume to total blood volume.

Two days later, his response to supine exercise was studied (table V). He increased his oxygen consumption to almost three fold and (table VI) his cardiac output increased; however, largely by virtue of his developing quite a tachycardia and not by virtue of an increase in stroke index. His arterio-venous oxygen difference (already somewhat wide at rest) widened quite markedly on exercise, and again this occurred with only a slight increase in central venous pressure. The blood volume was still lower than predicted and the ratio of central to total blood volume remained low. Administration of ouabain did not increase the low cardiac output, narrow the wide A-V difference, or lower the already normal right atrial pressure (table VII). From the normal response to exercise, and from the absence of a positive inotropic response to ouabain, we concluded that this low cardiac output state was not one of failure of the pump or heart failure, and postulated that the failure of the circulation was related to low blood volume and perhaps, also, to a shift in blood volume.

When we tilted this gentleman 60° head up, the heart rate rose to as high as 144 beats per minute in a 22-minute tilt (table VIII). The blood pressure fell rapidly. He complained of nothing, but he looked ashen and he did admit that he felt a little bit dizzy. He did not faint.

So much for this particular physiological state, which we feel may be just one of several in which the interrelationship between the variables mentioned might be studied profitably to gain better understanding.

Let me be the first one to present some studies of a female patient today. These studies have been largely stimulated by Dr. Dietlein who started us thinking about patients with chronic atrial dilatation as models of adaptation of possible stretch receptors in the atrial wall to chronic stimulation. We are interested in studying patients with mitral stenosis, but we are also particularly intrigued by the opportunities to study patients who are changing their atrial size and their atrial

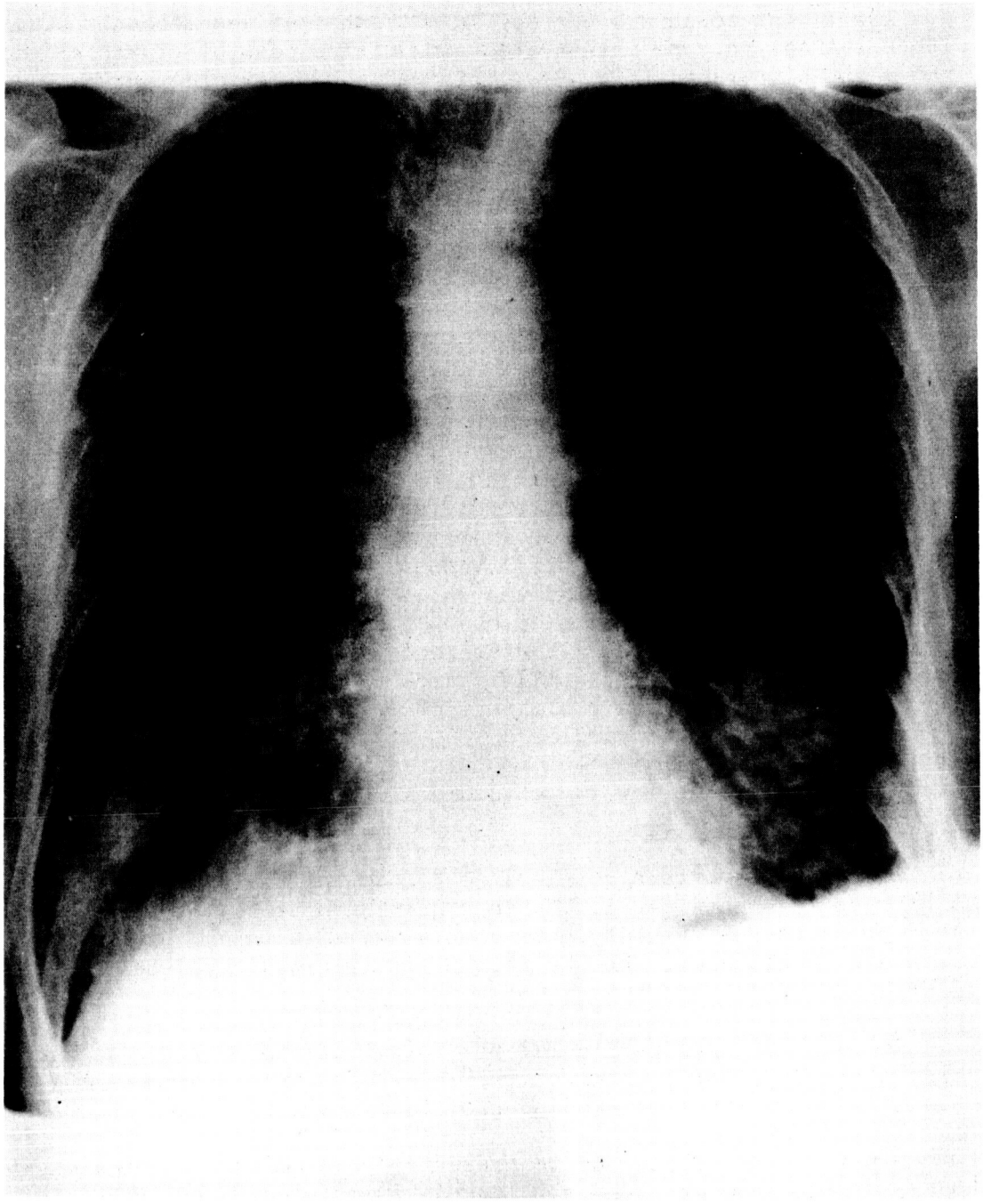

Figure 3.- Photograph showing rib structure of 62 year old patient.

TABLE IV.- FIRST STUDY: NOVEMBER 18, 1964

J.O. 62 M BSA 1.50 m^2 BCH No. 2024594

		Rest	100 percent O_2
Temp.	degree	97.5	97.5
Heart rate	b/min	85	80
Cardiac output	L/min	3.76	3.50
Cardiac index	L/min/m^2	2.51	2.33
Stroke index	cc/beat/m^2	29.6	29.1
Δ A-V O_2	Vol percent	6.49	
RA_m	mm Hg	2	2
BA_m	mm Hg	90	90
T. per. res.	dyne. sec. cm^{-5}	1915	2057
Bl. vol.	L	4.0	
CBV/TBV	percent	20.0	

TABLE V.- SECOND STUDY: THIRD HOSPITAL DAY

NOVEMBER 20, 1964

J.O. 62 M. BSA 1.50 m^2 BCH No. 2024594

		Rest	Exercise
Resp. rate		21	36
Min. vent.	L/min	7.9	22.9
O_2 cons.	cc/min	243	688
Vent. eq.	L/100 cc	3.2	3.4
pa O_2	mm Hg	68	66
Pa CO_2	mm Hg	34	35
pH		7.54	7.47
Sa O_2	percent	92.5	91.7
Hct.	percent	32.5	

TABLE VI.- SECOND STUDY: NOVEMBER 20, 1964

J.O. 62M BSA 1.50 m^2 BCH No. 2024594

		Rest	Exercise
Temperature	degree	99.5	100.0
Heart rate	b/min	96	145
Cardiac output	L/min	4.43	6.39
Cardiac index	$L/min/m^2$	2.99	4.32
Stroke index	$cc/b/m^2$	31.1	29.7
Δ A-V O_2	Vol percent	5.49	10.77
RA_m	mm Hg	3	6
BA_m	mm Hg	92	146
T. per. res.	dyn. sec. cm^{-5}	1661	1828
Bl. vol.	L	3.8	
CBV/TBV	percent	21.1	

TABLE VII.- SECOND STUDY: NOVEMBER 20, 1964

J.O. 62 M. BSA 1.50 m^2 BCH No. 2024594

		Control	Ouabain
Heart rate	b/min	96	106
O_2 consump.	cc/min	243	253
Cardiac output	L/min	4.43	4.07
Cardiac index	$L/min/m^2$	2.99	2.75
Stroke index	$cc/b/m^2$	31.1	26.0
Δ A-V O_2	Vol percent	5.49	6.22
RA_m	mm Hg	3	3
BA_m	mm Hg	92	80
T. per. res.	dyn. sec. cm^{-5}	1661	1572

TABLE VIII.- TILT STUDY: SIXTH HOSPITAL DAY

NOVEMBER 23, 1964

Rib Fractures, Pneumococcal Pneumonia (LLL)

J.O. 62 M. BCH No. 2024594

		Heart rate	Blood pressures - mm Hg	
		b/min	Systolic	Diastolic
Supine	21'	88	100	60
	25'	92	100	58
	30'	90	100	60
60° up	1'	96	70	46
	3'	116	90	0
	5'	116	90	58
	10'	120	80	58
	20'	124	60	40
	22'	144	64	46

function, particularly in relation to arrhythmias. Some of you know that one of the last publications by the late British cardiologist, Paul Wood (actually, Campbell published the observations posthumously), concerned observations on acute diuresis during supraventricular tachycardias. We were interested in studying the handling of a sodium load by patients with supraventricular arrhythmias, particularly atrial fibrillation, before and after conversion to regular sinus rhythm.

Table IX presents data obtained in the 48 year old lady known from previous hemodynamic studies to have mild mitral stenosis. With doctors Early and Tremblay, we studied the cumulative urinary sodium excretion expressed as percent of the load of 350 mEq. of sodium, infused in 2 liters, when the patient was in atrial fibrillation, on the day of electric cardioversion into a normal sinus rhythm, and a week afterwards. At the time of the initial study, there was rather poor excretion of the load on the first day, and the cumulative excretions for 4 days never reached one-third of the load. On the day of conversion, immediate excretion was lower, but the cumulative excretion reached a higher figure. Seven days later not only was the acute excretion a much higher one, but also the 4-day accumulation was certainly higher than when the patient was in atrial fibrillation.

Presumably we are dealing not only with a smaller atrium here, but also with a more pulsatile atrium. It is interesting to note that while we did not measure cardiac output in this lady before and after conversion, others have found that cardiac output and stroke volume may not increase until sometime after conversion. A look at our patient's pulses and blood pressures reveals that at approximately equal heart rates, (see table X) pulse pressure remained unchanged on the day of conversion, but rises after the infusion, concomitantly with the greatest rise in venous pressure observed. Seven days later, the initial pulse pressure was already greater at a relatively lower venous pressure, suggesting a larger stroke volume. It is planned to make simultaneous hemodynamic observations with future studies of sodium excretion to clarify this point.

I hope I have given an idea of the background from which we come, of the questions we are interested in, and of the bearing that our work may have upon some of the problems that have been brought out today.

TABLE IX.- UNINARY EXCRETION OF SODIUM LOAD

(350 mEq. in 2 L.) IN ATRIAL FIBRILLATION

AND AFTER CARDIOVERSION

A. A. 48 F. Mild Mitral Stenosis

	Cumulative		Urinary Na - Excretion percent of load	
	24 h	48 h	72 h	96 h
AF	12	28	28	28
NSR (day of conversion)	0.2	12	63	79
NSR (7 days after conversion)	21	45	53	56

TABLE X.- PULSE, ART. AND VEN. PRESSURES BEFORE (B) AND AFTER (A) SODIUM LOAD (350 mEq in 2 L) IN ATRIAL FIBRILLATION AND AFTER CARDIOVERSION

A. A. 48 F Mild Mitral Stenosis

		HR	BP - mm Hg			VP mm Hg
		b/min	Systolic	Diastolic	Pulse	
A.F.	B.	68	120	80	40	7
	A.	68	130	88	42	8
NSR (Day of conversion)	B.	64	120	80	40	9
	A.	69	140	70	70	11
NSR (7 days after conversion)	B.	72	120	60	60	6
	A.	72	130	60	70	9

BASIC CARDIOVASCULAR RENAL STUDIES

By Lawrence Earley, M.D.
Harvard Medical School

In our laboratory we have been interested in the mechanisms whereby the kidney regulates sodium excretion. This, of course, in a broader sense would involve the mechanisms of total extracellular fluid volume regulation. The pertinence of this to some of the problems that are faced at the Manned Spacecraft Center of NASA was not apparent to us until recently, but volume regulation, or at least the extracellular volume (as included in this, of course, the vascular volume) certainly is of importance in determining general or systemic hemodynamics and may be of particular importance to the orthostatic response under certain conditions. Certainly, after prolonged bedrest, which may be associated with diuresis and some contraction of the extracellular volume, the mechanisms regulating sodium are quite pertinent. We have been looking specifically at the kidney and the mechanisms involved in the renal regulation of sodium excretion, but this is a somewhat limited approach, and thus by joining efforts with Dr. Abelmann we hope that we can tie together systemic and renal hemodynamic changes which may be mechanisticly important in the regulation of sodium excretion and extracellular volume.

In terms of the kidney and how it can alter sodium excretion, there are two possible mechanisms: (1) the amount of sodium presented by filtration for tubular reabsorption can be altered so that decreases in filtration rate (which would diminish the filtered sodium) could reduce the excretion of sodium with no changes in tubular reabsorption; (2) on the other hand, the glomerular filtration rate and the amount of sodium excretion could be effected by changes in tubular reabsorption. Aldosterone is certainly one factor which can alter tubular reabsorption so that in the presence of a constant filtration rate, changes in aldosterone (that is, increases in aldosterone) would increase the level of tubular reabsorption and decrease the excretion of sodium. However, it is now well known that aldosterone may not be the major regulatory factor involved in bringing about changes in sodium excretion. Furthermore, it has been demonstrated during the past two years that aldosterone may be a relatively weak mediator of changes in sodium excretion compared to some of the unknown factors which must be involved in regulating the renal excretion of sodium. So we are left then with the possibility that other unidentified factors influence tubular reabsorption of sodium or that changes in sodium excretion are effected by a combination of changes

in filtration rate (or filtered sodium) and changes in aldosterone secretion.

The study shown on figure 1 demonstrates that there must be at least one other factor involved, and possibly several others which are not defined at all, factors other than filtration rate and aldosterone. These studies were performed in the dog who has been the blessing of the renal physiologists for many years, since the dog's kidney is qualitatively similar to the human kidney and quantitatively is closer to the human kidney than most other laboratory animals. In this type experiment, the animal is given a saline load (isotonic saline) and then the glomerular filtration rate is reduced by mild constriction of the ureter in order to drop it (GRF) to a level less than that existing prior to loading with salt when the excretion of sodium was relatively low. Then this ureteral constriction was progressively released to allow filtration rate to slowly increase. It was observed that the excretion of sodium increased progressively, and in fact reached a level of about 50 percent of the diuresing control kidney at a time when glomerular filtration rate (and filtered sodium) is still not above that which existed prior to infusing the load of saline. These animals were treated with large amounts of sodium retaining hormones so that fluctuations in aldosterone would presumably not influence sodium excretion. Therefore, this fraction of sodium excretion must be brought about by some change in tubular reabsorption of sodium which is not mediated by aldosterone.

Changes in sodium excretion relate to changes in extracellular volume, and there is abundant evidence that the regulation of extracellular volume (which includes, of course, the vascular volume) is dependent on the regulation of sodium excretion. Although water is the true determinant of volume, the regulation of water balance will follow secondarily so long as the pituitary-antidiuretic hormone system is intact. Observations such as the one shown here led us to look at a different parameter of renal function which might relate to the regulation of sodium excretion. We were eager to find possible relationships between renal blood flow and sodium excretion, since this would be a connection, perhaps, with systemic hemodynamics and sodium excretion.

Utilizing the clearance and the renal extraction ratio of PAH one can calculate, by a modification of the Fick formula, total plasma flow, and then from the hematocrit total blood flow (fig. 2). We found the extraction ratio of PAH diminishes during expansion of the extracellular volume (isotonic saline infusion), and in all cases total renal blood flow increases during the time of increased sodium excretion.

On figure 3 is shown an experiment in which observations were made before, during, and after saline infusion. Under these conditions, a spontaneous dissociation between changes in filtered sodium and changes in blood flow may occur, yet, a parallelism always existed between

NASA-S-65-3462

SPACE MEDICINE BRANCH
RESEARCH COORDINATION MEETING

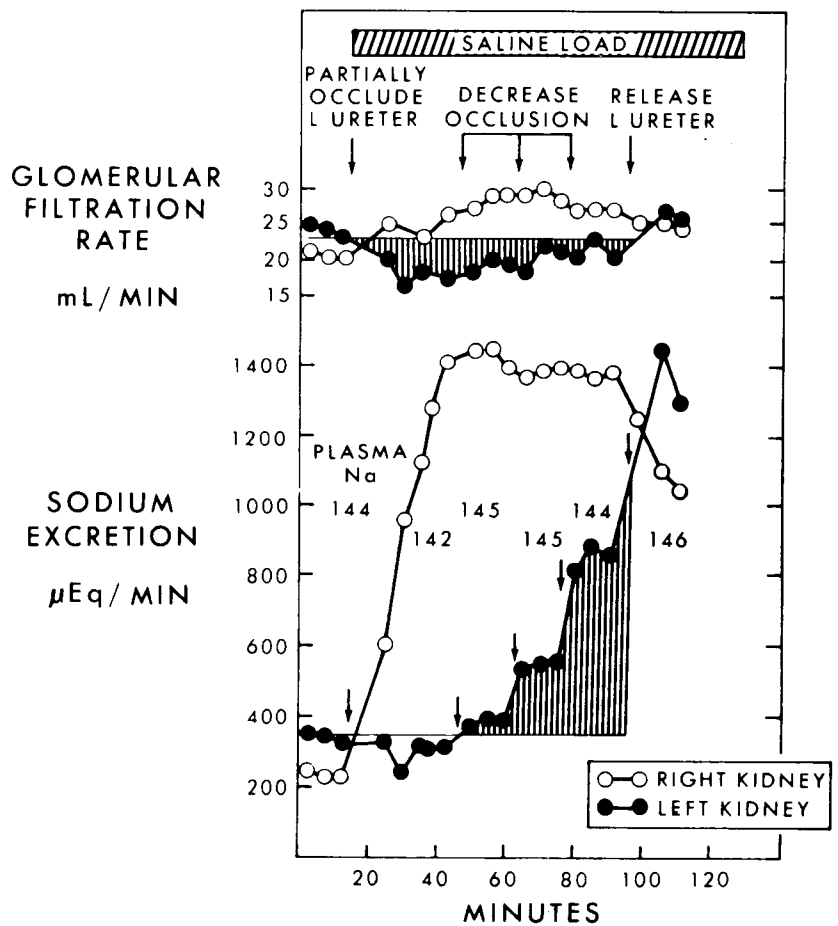

Figure 1.- Glomerular filtration rate and sodium excretion.

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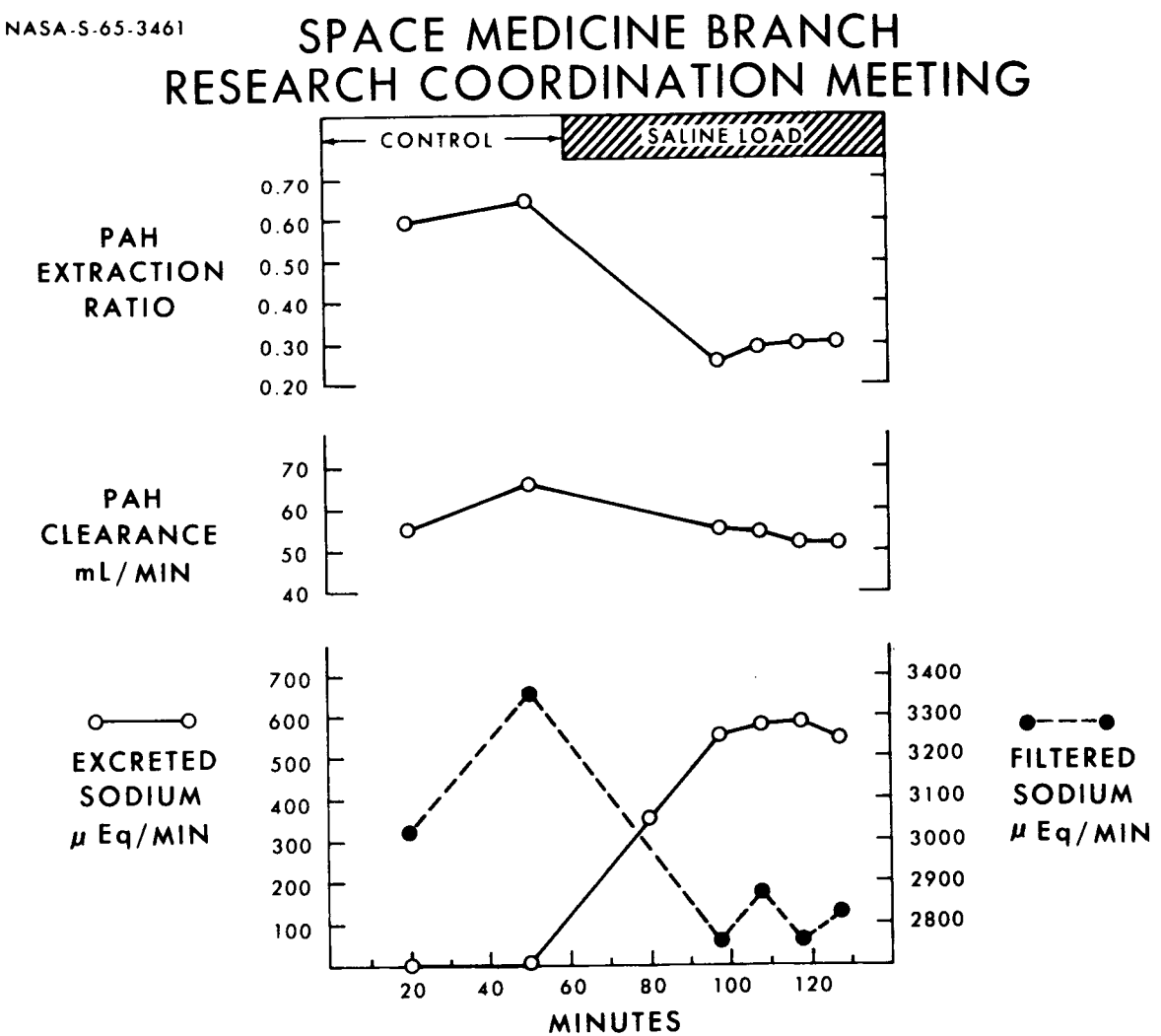

Figure 2.- PAH extraction ratio, PAH clearance, and excretal sodium.

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SPACE MEDICINE BRANCH RESEARCH COORDINATION MEETING

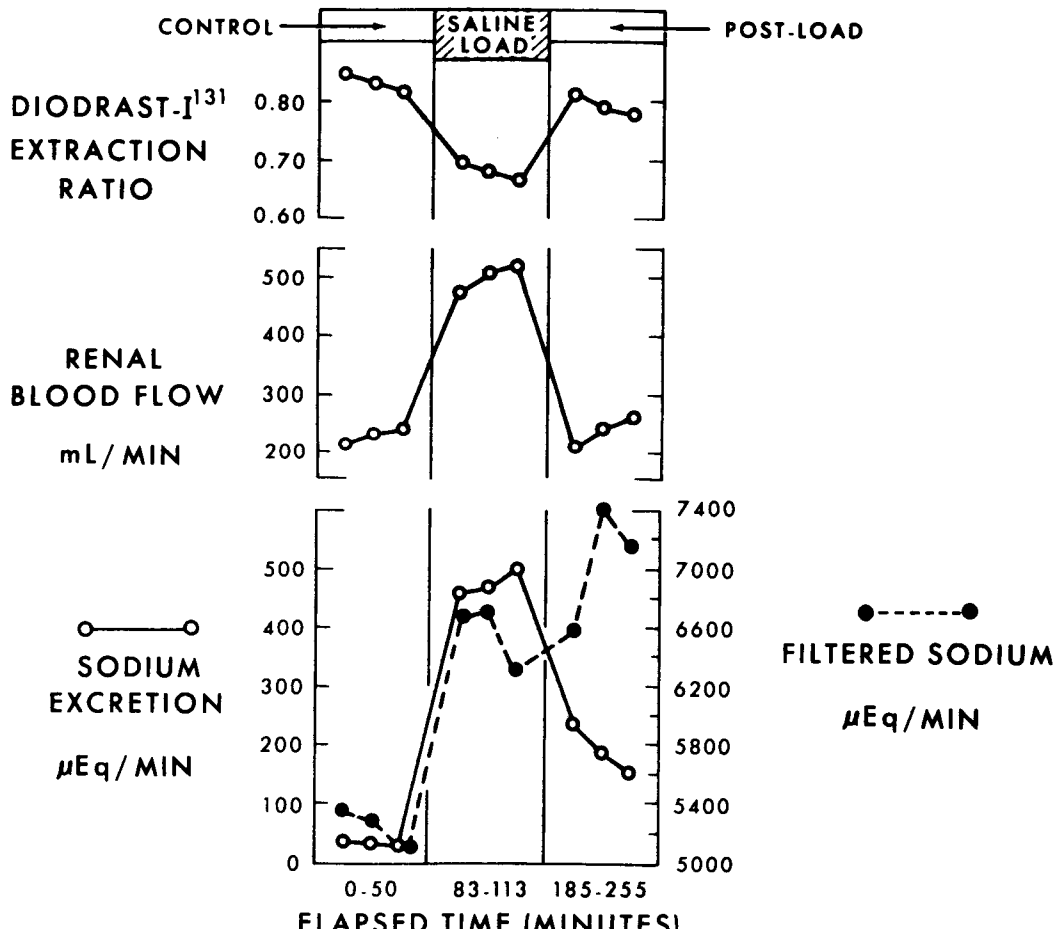

Figure 3.- Diodrast extraction ratio, renal blood flow, and sodium excretion.

changes in sodium excretion and changes in blood flow. As shown, the animal prior to infusion of isotonic saline had a very low rate of sodium excretion which increased abruptly during the period of saline loading. The filtered sodium which in this case is represented as the glomerular filtration rate, increased in parallel with the increase in sodium excretion, or in this case diodrast extraction, and the usual increase in renal blood flow. Following the period of saline infusion, sodium excretion returned back toward the low pre-loading control levels. However, the filtered sodium continued to increase, indicating that this drop in sodium excretion did not relate to a drop in the filtered load of sodium. Renal blood flow on the other hand, did return back to the control level and the extraction ratio of diodrast returned toward control. So in this type of experiment, there can be demonstrated a spontaneous relationship between renal blood flow and sodium excretion, independently of changes in the glomerular filtration rate.

It has been stated frequently in the literature that both man and the dog may not increase the glomerular filtration rate in association with increased sodium excretion during saline loading (fig. 4). More recently this has been documented to the extent that this appears unequivocal, and we have noted this in several experiments. In this demonstration, the filtered sodium prior to infusing saline was at these low levels. After infusing saline, not only did it (GFR) not increase, but it actually fell to a level less than that prior to the infusion of saline. Despite this failure of GFR to increase, sodium excretion increased, and the extraction ratio of PAH decreased strikingly. Therefore, increased renal blood flow accompanied this natruresis even though there was no increase in GFR.

These studies have been extended, and we have more recently been manipulating blood flow during saline loading. By constricting the aorta between renal arteries and reducing blood flow to one kidney, sodium excretion can be decreased as small decreases occur in blood flow without alterations in the filtration rate. The changes that we have found in the extraction ratio of PAH and diodrast, we feel may be indicative of changes in the distribution of blood within the kidney. Since these substances are extracted primarily, or as far as known, entirely by the renal cortex, then decreases in the ratio of the extraction would suggest more of the nutrient blood reaching the kidney is going to areas other than the cortex. This fraction of blood could include flow to the renal medulla.

In the future we plan to continue these studies in the dog, and also to make observations in human situations in which there are abnormalities in volume regulation and/or systemic hemodynamics in an effort to observe additional correlations between systemic and renal hemodynamics and sodium excretion.

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SPACE MEDICINE BRANCH
RESEARCH COORDINATION MEETING

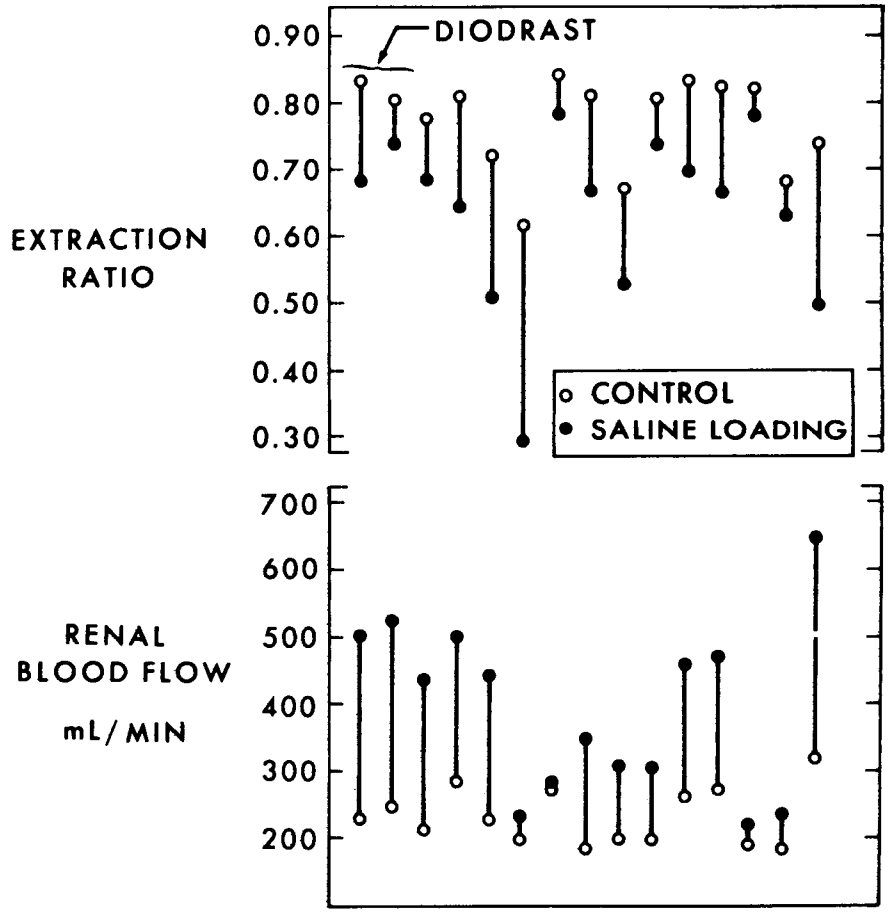

Figure 4.- Extraction ratio and renal blood flow.

THE EFFECTS OF DRUGS ON POST-RECUMBENCY ORTHOSTATIC INTOLERANCE

By Kenneth H. Hyatt, M.D.
USPHS Hospital, San Francisco, California

We have recently become involved with the NASA program of studying cardiovascular deconditioning and up to this time, we have been acquiring necessary additional equipment, setting up procedures, and preparing to start our study. We plan to initiate our study shortly after the beginning of 1965. At the present time, my remarks must be limited to giving you a brief rundown on what we plan to do and how we plan to go about doing it.

Our major objectives are to attempt to further delineate in detail those changes in cardiovascular, renal, and autonomic function, which are responsible for the so-called cardiovascular deconditioning that occurs following bed rest. We feel that of these effects, the autonomic changes are probably the most poorly understood. Certainly, at the meeting in San Antonio a few weeks back, it seemed apparent to me that one could not specifically relate these changes to alterations in plasma volume.

The first 2 days of hospitalization will be used as an orientation period for the patient. During this time, we will explain the proposed study to the subject in greater detail, introduce him to the instrumentation which will be used in the study, and have him perform dry-run urine and stool collections. On the first day of the orientation period, he will be placed on a formulated diet. He will remain on this diet until the end of the period of bed rest.

We have divided the study into three phases: a control phase, a bed rest phase, and a recovery phase. We will have three groups: a control group, a second group in which we plan to induce chronic plasma volume expansion by using 9-alpha-fluoro-hydrocortisone, and a third group that will do arm and leg exercises on a Lanoy bicycle ergometer against a workload of 30 watts, for 10 minutes, 3 times daily.

Plan of Study

PHASE I: Control Phase.- During the control period, we will measure the patient's weight, arm, thigh and leg diameters daily. His temperature, pulse, respiration, and blood pressure will be measured four times daily. The control period will begin after the patient has been on the formulated diet for a minimum of 48 hours. On the day prior to beginning the control period, we will subject the patient to a 70° tilt. At this time we will follow changes in blood pressure, heart rate, respiration, phonocardiogram, and lower extremity volume. On the first day of the control period, we will do the following blood work: CBC and sedimentation rate, serum proteins, serum sodium, potassium, chloride, phosphate, calcium, magnesium, osmolality, and creatinine. Blood volume and cardiac output will be measured. A sample will be drawn for serum catechol amines. On days 1 and 2 of the control phase, 24-hour urines will be collected for sodium, potassium, chloride, phosphate, calcium, magnesium, nitrogen, creatinine, creatine, osmolality, 17 hydroxycorticosteroids, and aldosterone. On day 3 of the control phase, 24-hour urine will be collected for sodium, potassium, chloride, phosphate, calcium, magnesium, nitrogen, creatinine, creatine, and osmolality. On days 4 and 5 of the control phase, 24-hour urines will be collected for sodium, potassium, chloride, phosphate, calcium, magnesium, nitrogen, creatinine, creatine, osmolality, and catechol amines. On day 6 of the control phase, 24-hour urines will be collected for all of the standard chemistries mentioned above; that is, excluding catechol amines, 17 hydroxycorticosteroids and aldosterone. On this day, renal clearance of PAH, inulin, electrolytes, and osmolality will be determined. The data from these clearances will be pooled with the 24-hour urine to give total output.

To return to day 1 of the control phase, the patient will be given a carmine label orally. On appearance of this label in the stool, three day pooled stool collections will be started. These will be collected until such time as a second carmine label, which will be given on the first day of the bed rest phase, appears.

Day 7, or the final day of the control phase, will be utilized for cardiac catheterization. Standard right heart catheterization will be performed with a catheter being placed in the pulmonary artery and a Cournard needle in the brachial artery. Following the placement of the catheters, we will measure the blood volume of the patient and draw a sample for serum catechol amines. Utilizing the usual means of measuring pulmonary and peripheral arterial pressures and mean pressures and performing cardiac outputs, we will obtain data which can be used to calculate resistances, stroke volume, and control blood volume. A Whitney-type strain gauge will be utilized to measure changes in limb volume and blood flow during the state of cardiac catheterization.

In order to insure that the data mentioned above is basal, we will determine minute ventilation on the day prior to cardiac catheterization. On the day of cardiac catheterization, minute ventilation will be redetermined until a stable basal state is reached. The data mentioned above will then be collected.

Following the determination of basal hemodynamic data, the patient will be placed in a 70° tilt position. Hemodynamic measurements will be repeated at an appropriate time following the beginning of tilt. Serum cathechol amines will also be drawn at this time. The tilt will be interrupted just prior to fainting or if possible the patient will be kept in the tilt position for a minimum of 20 minutes. At the end of 20 minutes, the patient will be returned to the supine position and allowed a suitable recovery period.

Following the recovery period, the patient will perform exercise in supine position on a Lanoy bicycle ergometer. We plan on imposing a 30-watt workload which is equivalent to light exercise. Once a steady state is reached, our hemodynamic data will be repeated. Attempting to obtain at least some of the data that the group from TIRR has been working on (after the completion of steady state exercise), we will follow their procedure of increasing the workload by 10-watt increments until the heart rate has reached 180. At this point, we will cease exercise and follow the fall in heart rate and blood pressure to normal levels. We will then allow the patient a 15-minute rest period. At the end of this time, we will have the patient void and urine will be saved for catechol amine analysis. We will then inject tyramine intravenously. Blood pressure, heart rate, electrocardiogram, will be monitored continuously following injection of tyramine and at the peak response, cardiac output will be measured. Subsequent to the injection of tyramine, two 1-hour urine collections will be made. Urinary catechol amines will be determined on these specimens. At the peak of blood pressure response following injection of tyramine, a sample will be drawn for serum catechol amines. Our purpose in doing this is to attempt to determine the status of norepinephrine stores in post-ganglionic adrenergic nerve endings. In a normal person, we would expect that we would have a rise in serum norepinephrine as well as a rise in blood pressure and heart rate. This rise in serum norepinephrine would be reflected by an increased outpouring of urinary norepinephrine in the 1 to 2 hours following injection of the tyramine. With diminished, or in some manner immobilized norepinephrine stores, there should not be a rise in either the blood pressure on the serum or plasma or urine norepinephrine levels. If, on the other hand, the stores in the individual are normal but his receptors are not functioning properly, we would expect that his plasma and urine norepinephrine levels would rise but that there would not be a concomitant blood pressure rise. Thus, we hope, by utilizing tyramine, that we may be able to determine something about peripheral norepinephrine stores.

PHASE II: Bedrest Phase.- The patient will be placed on absolute bed rest for a period of 2 weeks. During this time, we will continue to monitor the parameters that were mentioned under the control phase; that is, the various urine, fecal, and plasma measurements. We will also periodically monitor blood volume and cardiac output. Urinary clearances will be determined each week of bed rest to allow calculation of renal plasma flow and glomerular filtration rates. On day 15 of bed rest, we will repeat the studies done on day 7 of the control period; that is, we will repeat cardiac catheterization on the patient and repeat the studies outlined above.

PHASE III: Recovery Phase.- Our present plans are to discontinue the formula diet at the end of the bedrest phase. We will continue to monitor physiologic changes and the patient's response to 70° tilt, following termination of the bed rest period. As the study progresses, we hope to keep some subjects for a period longer than 4 weeks. This will allow us to continue the formula diet for a period of up to 1 week following bed rest and determine the recovery rate of various metabolic parameters.

HEMODYNAMIC RESPONSE TO ACUTE HEAT STRESS IN NORMAL MALES

S. H. Lau, M.D.
USPHS Hospital, Staten Island, New York, New York

Our project is concerned with studying the hemodynamic responses to acute heat stress in normal male subjects prior to and following a period of immobilization. Relatively few well controlled studies have been performed which evaluate the cardiovascular system's adjustment to such thermal stress. In addition, we are unaware of any studies which have evaluated the combined effects of acute thermal stress and immobilization on the cardiovascular system.

In 1957 Burch and Hyman reported the effects of acute heat stress on seven subjects, three of whom were normal controls and four subjects were in the state of congestive heart failure. These investigators reported a three to fourfold increase in cardiac output and amazingly high values for increases in stroke volume. They also reported that the calculated work of the left ventricle was increased. In contrast to these findings, Sancetta (1958), reporting on 16 subjects, only one of whom was normal, found no significant change in cardiac output, oxygen consumption, or A-V oxygen differences. Calculated left ventricular work in their patients decreased. In both of the above studies, the subjects were evaluated in the supine resting position utilizing cardiac catheterization procedures.

A review of the literature since 1958 confirms the need for a normative study on the cardiovascular system's adaptive mechanisms to acute heat stress in unacclimatized as well as acclimatized individuals in various age groups. Similarly the effects of deconditioning (2 weeks bed rest) when added to the state of acute heat exposure have been insufficiently studied.

We plan to study normal male volunteers exposed to acute heat stress prior to and following a 2-week period of bed rest. Subjects will be studied at a temperature range of 70° F to 110° F at a relative humidity of 45 percent. Cardiac catheterization and the Fick method will be used to measure cardiac output, oxygen consumption, A-V oxygen difference, calculated stroke volumes, pulmonary and systemic vascular resistances and pressure. Measurements will be made both at rest and during exercise. Skin and rectal temperatures will be recorded.

Our environmental test chamber is in the process of being built and it is hoped that we may begin our study about March 1, 1965.

PROTON IRRADIATION METABOLIC AND ULTRASTRUCTURAL EFFECTS

Gilbert Cherrick, M.D.
Seton Hall College of Medicine

Many biologists have had the seemingly well justified concern that high energy protons emanating from solar flares may be a significant source of radiation exposure to astronauts during the course of a prolonged space journey. Although a great deal of information has been collected about the biologic effect of X-rays and gamma rays, very little has been learned about the effects of high energy protons. Until very recently, that information seemed to have very little practical importance. With the coming of distant space travel, it would now seem to have considerable importance.

Dr. Carroll Leevy and myself, at the Seton Hall College of Medicine, have been interested in factors which induce liver cell injury and liver regeneration. From this background stemmed our interest in how and to what degree high energy protons may injure the liver and the sequence of events which might then occur. The liver is a suitable organ for study in this way since it has at least 3 well defined cell types (parenchymal, mesenchymal, and ductular), the turnover rates of which have been extensively studied. Also, the liver is the site of many metabolic processes which can serve as convenient markers for studying the harmful effects of radiation.

Observations and Measurements Following Hepatic Proton Irradiation

1. Morphologic changes (light and electron microscopic)
2. DNA synthesis (in vitro autoradiographic techniques)
3. DNAse, pyruvic transaminase
4. Folate, N^5 formyl tetrahydrofolate, B_{12}, pyridoxine, nicotinamide, riboflavins
5. DPN, DPNH
6. Amino acids and nitrogen

Figure 1

As seen on figure 1, in our initial pilot study, we have made the following observations and measurements following hepatic proton irradiation: (1) light microscopic studies to determine whether major evidences of tissue injury are present (2) electron microscopic studies to determine whether more subtle evidences of tissue injury (for example, mitochondrial swelling and distortion of endoplasmic reticulum) have occurred (3) DNA synthesis, as measured by an in vitro autoradiographic technique (4) DNAse (5) pyruvic transaminase (6) levels of the

vitamins: folate, N^5 formyl tetrahydrofolate, B_{12}, pyridoxine, nicotinamide, and riboflavine (7) the pyridine nucleotides DPN and DPNH (8) amino acids and (9) nitrogen.

We have recently irradiated one group of animals at Harvard University, using the 160 MeV cyclotron which is located there, with 1000 rads of protons. That cyclotron is admirably suited to our purpose for the reason that it produces a beam, the axial dose of which is linear over several centimeters. As seen on figure 2, the radial dose along that portion of the beam is linear for about 4 millimeters. We can therefore evenly irradiate a mass of tissue sufficient for all of our measurements.

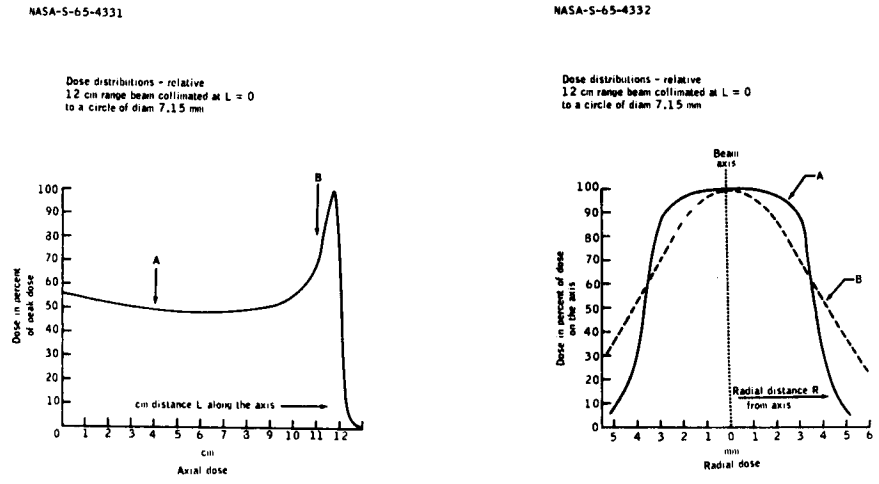

Figure 2.- Dose distributions – relative 12 cm range beam collimated at L = 0 to a circle diameter 7.15 mm.

Before the animals are irradiated, the position of the liver is delineated on X-ray pictures following the induction of a small pneumoperitoneum. The air provides a good contrast for the liver tissue and permits accurate localization of it. An X-ray picture of the Sprague-Dawley rat, such as we use, is shown on figure 3.

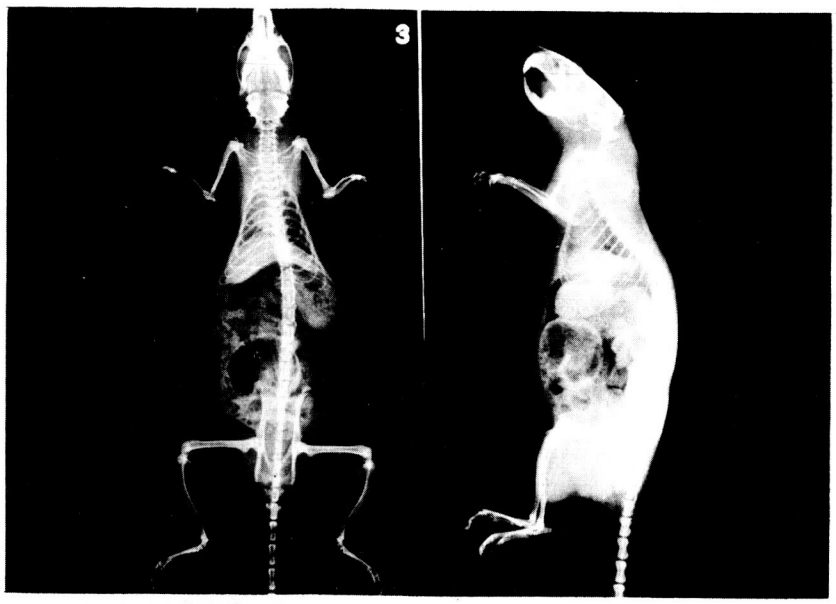

Figure 3.- X-ray picture of a Sprague-Dawley rat.

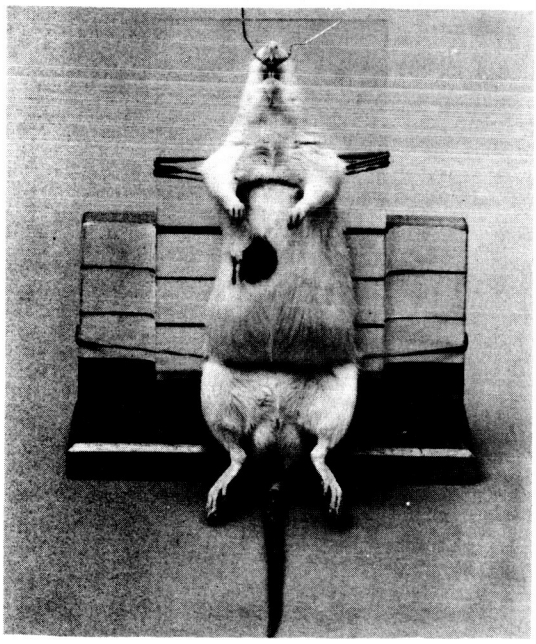

Figure 4.- Rat prepared for placement in the cyclotron beam.

The animals are prepared for irradiation with Librium tranquilization. This drug produces no changes in the enzymes or coenzymes, which we measure subsequently. The rat is then placed on a mounting rack; the collimator of the cyclotron is aimed at the mark on the anterior abdominal wall which overlies the portion of the liver in the right upper lobe selected for irradiation. Figure 4 shows a rat prepared for placement in the cyclotron beam. The beam enters through the anterior abdominal wall, traverses the liver (avoiding kidney, stomach, and intestine) and then passes through the posterior body wall.

As seen on figure 5, one can locate the tissue which has been exposed to the cyclotron beam. The X-ray plate, placed behind the animal, is exposed to 5 rads of protons. This produces a white circle on the X-ray picture which is then made of the animal's body.

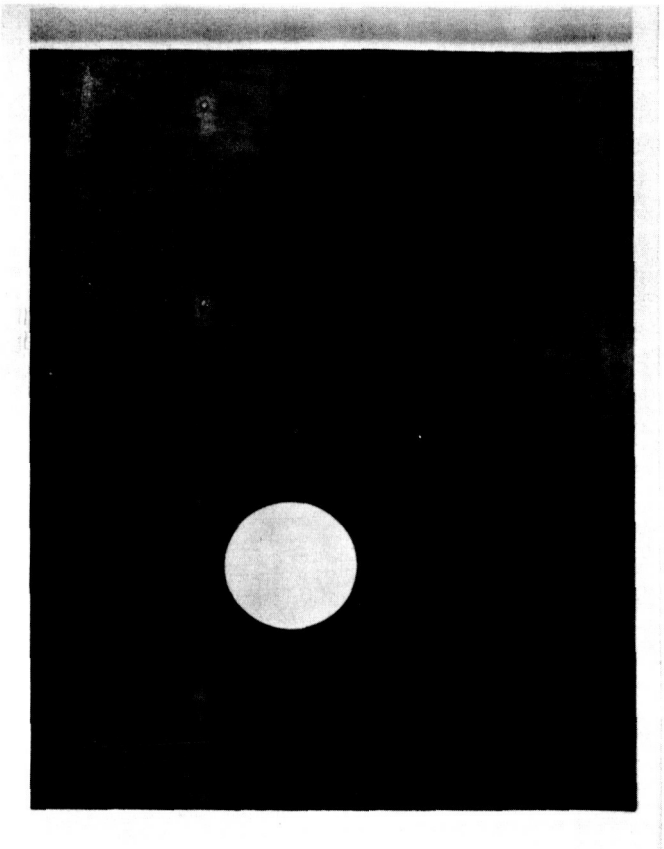

Figure 5.- Tissue location which has been exposed to the cyclotron beam.

After the animals have been irradiated in Cambridge, Massachusetts, they are brought to our laboratory in Jersey City where they are killed at intervals. That portion of tissue which had been irradiated is then removed and analyzed. We are currently studying animals which had been exposed to the 1000 rad proton dose.

I would now like to tell about another area of investigation, which has been of interest to my colleagues, Dr. Carroll Leevy, Dr. Maceo Howard, and to me: the effect of postural changes on the splanchnic circulation. We have used the dye, indocyanine green, for the past 6 years

in the Fick principle measurements of splanchnic flow. Indocyanine green is well suited for this purpose since it is not removed from the circulation by extrahepatic mechanisms; undergoes no enterohepatic recirculation; and is not conjugated. One can record levels of circulating dye by means of a dichromatic densitometer, set to absorb maximally at 810 millimicrons, the absorption maximum of indocyanine green. That instrument with its earpiece which monitors dye flowing through external ear capillaries is shown on figure 6.

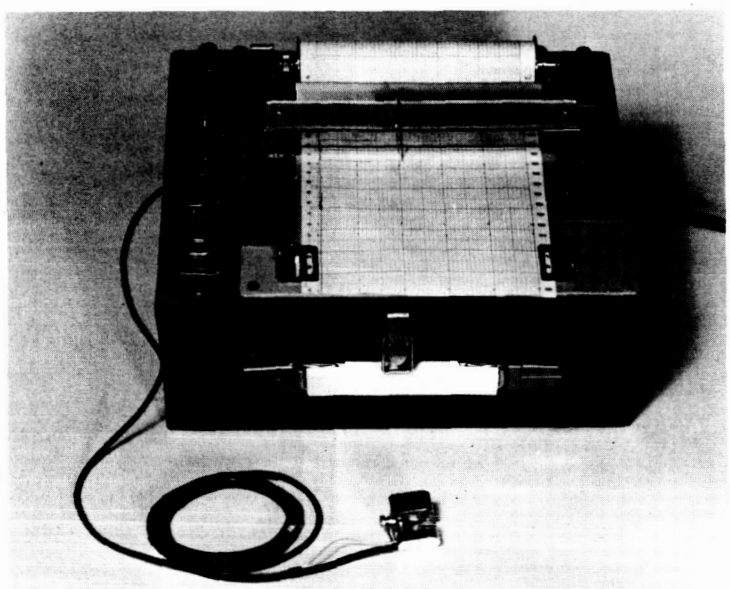

Figure 6.- Dichromatic densitometer.

Following a single intravenous injection of the dye, there follows a period when the dye disappears from plasma exponentially. That early portion of the dye disappearance curve is a function of splanchnic blood flow; satisfactory estimates of splanchnic flow can be made from it.

By using ear densiotometry measurements of indocyanine green, one can study splanchnic blood flow during the administration of agents which influence it. As shown on figure 7, pituitrin caused the arterial level of indocyanine green to rise in a patient with Laennec's cirrhosis. It is seen that the extraction ratio of the dye (determined during hepatic vein catheterization) did not change. The increased arterial blood concentration of the dye is therefore a function of decreased splanchnic blood flow.

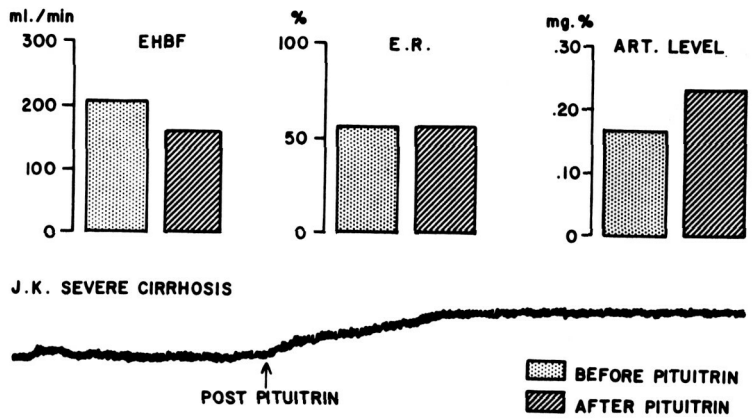

Figure 7.- Pituitrin caused the arterial level of indocyanine green to rise in a patient with Laennec's cirrhosis.

As seen on figure 8, we have done some preliminary studies on the effect of posture on the plasma disappearance of this dye during the course of a constant infusion. When the subject stands, arterial dye level rises. When the subject sits, dye concentration reaches a level between those characteristic of standing and recumbent positions. We are investigating the possibility that these positional changes in dye concentrations are purely a function of decreased splanchnic blood flow. It is conceivable that they may occur as the result of altered extraction ratio as well. The pituitrin studies suggest the liklihood of the former possibility. We hope that our continuing experience with such studies of the splanchnic circulation will shed light on the altered circulatory physiology resulting from immobilization, a problem to which many of you have referred today.

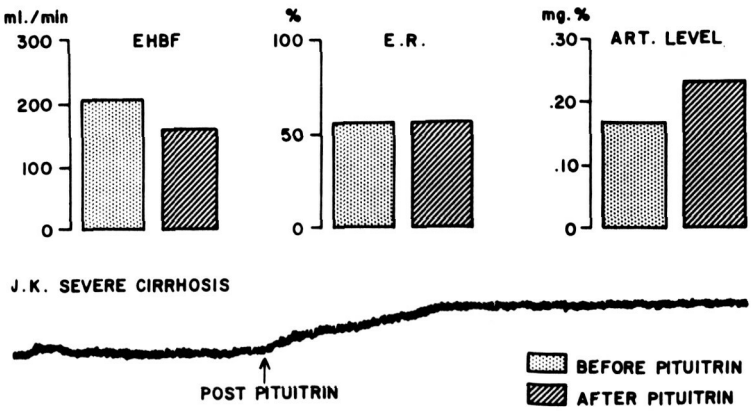

Figure 8.- Effect of posture on the plasma disappearance of indocyanine green during the course of a constant infusion.

MATHEMATICAL EXPRESSION OF THE ARTERIAL PRESSURE PULSE CONTOUR IN MAN

Thomas B. Watt, Jr., M.D., Ph.D.
U.S.V.A. Hospital, Houston, Texas

Observations of human arterial blood pressure p versus time t curves have suggested a descriptive model for the contour of the dicrotic portion of each pulsation. This model,

$$p(t) = \alpha_1 + \alpha_2 e^{-\alpha_3 t} + \alpha_4 e^{-\alpha_5 t} \cos(\alpha_6 t - \alpha_7),$$

superposes a damped harmonic oscillation ($\alpha_4 e^{-\alpha_5 t} \cos(\alpha_6 t - \alpha_7)$) upon a logarithmic decay ($\alpha_2 e^{-\alpha_3 t}$) to some end value of pressure (α_1) not necessarily zero. Assuming this form for $p(t)$, a digital computer was programed to determine the α_i which achieves a least squares approximation to a pressure curve recorded from a brachial artery cannula in an actual patient. Figure 1 shows this model curve fitted to data obtained from a "normal" patient (that is, a patient screened for absence of cardiovascular disease) and from two distinctly abnormal patients. Comparative values for the α_i are given in table I. On the average, the standard error between points along an actual arterial pressure curve and its least squares approximation was about 1 mm of mercury.

To establish a more than intuitive relationship between values of α_i and constants having overt physical significance, the lumped parameter electrical analog shown in figure 2 was postulated [1]. The analog depicts elastic reservoirs (represented by C_1 and C_2) situated at each end of a column of blood with inertia (represented by L). All dissipation of energy and resistance to flow are assumed to be concentrated in the capillary bed (represented by R) into which the terminal elastic reservoir (represented by C_2) discharges. v_1 (portraying $p(t) - \alpha_1$) and v_2 of the analog indicate the effective instantaneous pressures in the elastic reservoirs and i represents the effective instantaneous

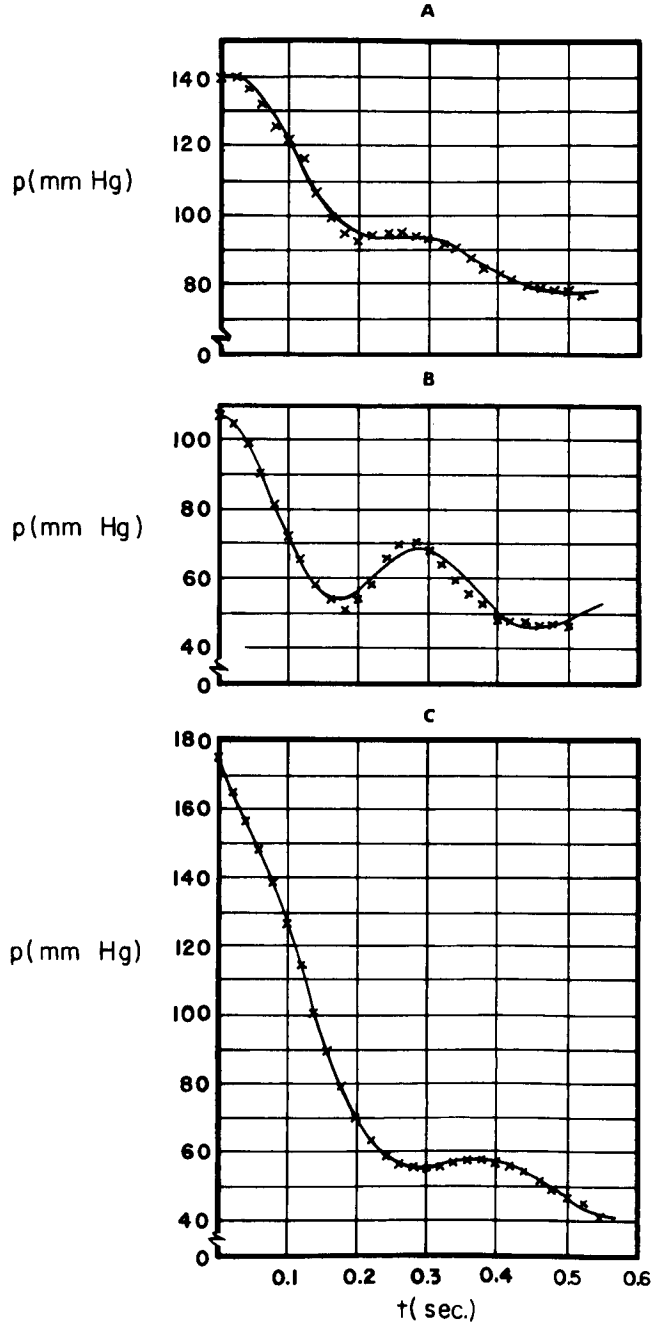

Figure 1. Models of human arterial blood pressure (p) versus time (t) curves from a normal, a cardiomyopathy, and an aortic insufficiency patient.

TABLE I.- COMPUTED MODEL PARAMETERS α_i FOR SELECTED PATIENTS

Clinical status of patients of figure 1							
	α_1	α_2	α_3	α_4	α_5	α_6	α_7
A. "Normal"	68.5	68.9	3.86	-13.2	4.07	23.6	-1.73
B. Cardiomyopathy	38.9	47.8	3.06	21.7	2.74	22.6	0.541
C. Aortic Insufficiency	41.5	140.5	7.01	-21.6	3.27	19.8	-1.32

flow between the reservoirs. The analog system parameters (C_1, C_2, L, and R) have been calculated from α_3, α_5, and α_6 derived above and the resultant system simulated on an analog computer. Two normal modes of free oscillation can occur simultaneously in the analog. Suitable initial conditions for v_1, v_2, and i (representing the state of the system at the end of the anacrotic portion of the pressure curve) have next been calculated from the α_i such that the resultant $v_1(t)$ is identical to $p(t) - \alpha_1$. These initial conditions provide the proper linear combination of the normal modes required to duplicate the least squares approximation of the brachial artery pressure curve of the patient.

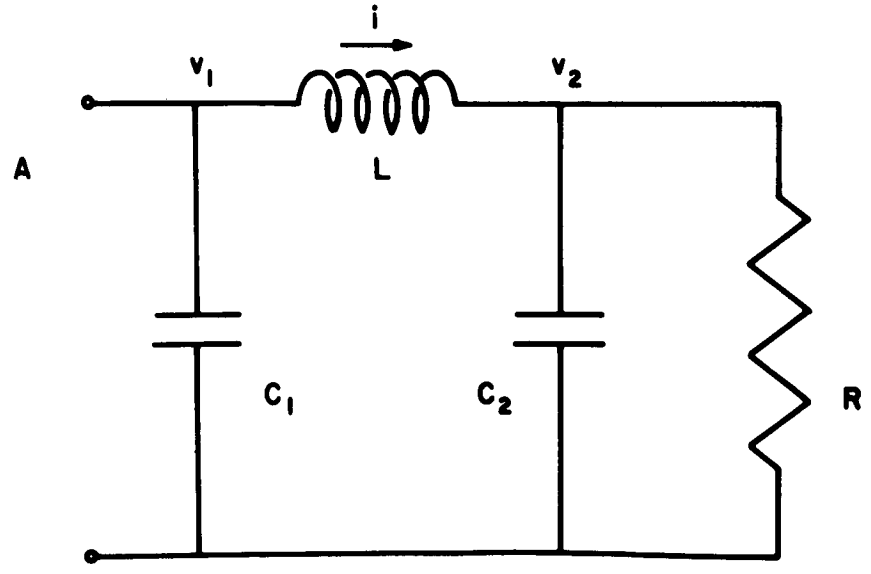

Figure 2. Lumped parameter electrical analog depicting elastic reservoirs and inertia.

As an example, figure 3 represents a simulated curve corresponding to A of figure 1. The individual modes of oscillation are also indicated on this figure. Here calculated parameters are R = 1.000, C_1 = 0.190, C_2 = 0.083, and L = 0.029. Initial conditions are $v_1(0)$ = 71.0, $v_2(0)$ = 56.8, and i(0) = -6.30. As a note, some of the

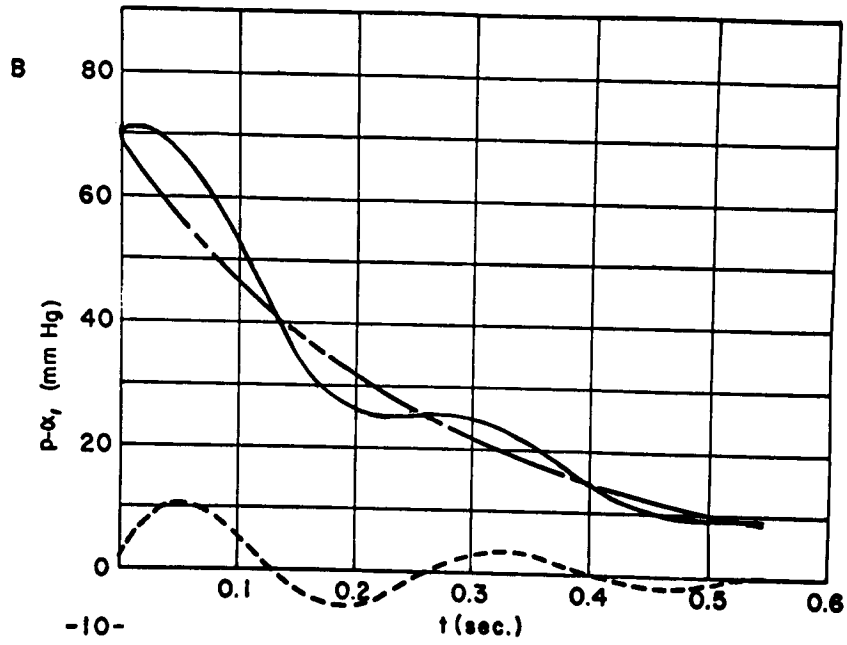

Figure 3. Simulated curve corresponding to A of figure 1.

curves obtained for i(t) have qualitatively resembled published curves of instantaneous blood flow [2].

It is appropriate to discuss the analog of figure 2 in the light of previous related work. Based on papers of the mathematician Leonard Euler, O. Frank [3] proposed a theory of the circulation better known from its German origin as the "Windkessel" theory. In this model, an elastic reservoir discharges into a simple peripheral resistance. While gradually decreasing loss of pressure during diastole can thus be described, any further undulations along the dicrotic limb of the pressure curve cannot be represented. Conversely, the transmission line model first proposed by Moens and Korteweg [4] regards the arterial system as a network of tubing through which pressure waves are transmitted and reflected, thus permitting the undulations observed in the pressure curve during diastole. However, the complexity of this model has limited its clinical usefulness. Our model and its analog of figure 2 are a compromise between the elastic reservoir model and the transmission line model in an attempt to explain the undulations in a relatively simple and useful manner.

The significance of these results resides in the possibility provided for studying variations in elastic, inertial, and resistive

properties encountered in human circulation under diverse conditions of stress or disease. Further investigations are directed toward definition of the normal range for both system parameters and initial conditions, determination of changes which may result from cyclic respiration or from induced physiologic or pharmacologic stresses, and identification of abnormal values associated with specific disease states (for example, untreated and treated hypertension, valvular or myocardial disorders of the heart, or the general problems of vascular aging and arteriosclerosis). In addition to these clinical studies, theoretical extensions are under consideration.

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7. Figure 1. Computed least squares approximation (solid line) compared to actual measured patient arterial pressure data (x-marks) of dicrotic portion of brachial artery pressure curve for A, J. H., a "normal" patient, B, L. S., a cardiomyopathy patient, and C, E. D., an aortic insufficiency patient. Comparative values of α_i are noted in table I.

8. Figure 2. Lumped parameter electrical analog for the vascular system - see text for symbol interpretation.

9. Figure 3. Normal modes of free oscillation of analog (broken lines) which add to yield composite curve (solid line) identical to least squares approximation of figure 1.

10. Roger M. Goldwyn, Ph.D., of the Department of Electrical Engineering at Rice University contributed to the work being presented in the paper.